cancer treatment reports

Cumulative Subject and Author Indexes: 1966-1975

Volume 62
Number 4
April 1978
Pages 493-672

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

cancer treatment reports

National Cancer Institute, Arthur C. Upton, *Director*

Division of Cancer Treatment, Vincent T. DeVita, Jr., *Director*

Editorial Board

Bruce A. Chabner, *Editor-in-Chief*
Associate Editors:
Paul A. Bunn
Michael Colvin
David A. Cooney
John S. Driscoll
Marc E. Lippman
John S. Macdonald
Stephen C. Schimpff
Susan M. Sieber
John L. Ziegler

Editorial Staff

Pamela W. Jones, *Managing Editor*
Jean Griffin Baum, *Assistant Editor*
Elaine P. Beck, *Assistant Editor*
Virginia T. Ascosi, *Editorial Assistant*
Florence L. Barnes
Mary M. Davis
Deidre A. Hoehn

Advisory Board

Bernard Fisher
Emil J Freireich
Lewis W. Guiss
Simon Kramer
Faith H. Kung
LaSalle D. Leffall, Jr.
John A. Montgomery
David G. Nathan
Paul E. Neiman
Stanley E. Order
Theodore L. Phillips
Philip Rubin
Edward F. Scanlon
Stuart F. Schlossman
Joseph V. Simone

Editorial Policy

The Editorial Board will consider manuscripts dealing with all aspects of preclinical and clinical cancer treatment. These may include such topics as surgery, radiotherapy, chemotherapy, immunotherapy, supportive care, pharmacology, cell biology and kinetics, mechanisms of drug action, and medicinal chemistry.

The journal will consist of two parts. One part will consider previously unpublished manuscripts of original work under four main categories:

1. **Clinical or preclinical research.**
2. **Correspondence regarding manuscripts previously published in *Cancer Treatment Reports*. Letters on other topics will be published at the discretion of the Editorial Board.**
3. **Invited guest editorials and reviews. Unsolicited contributions will be considered on their individual merits.**
4. **Brief communications. Under this category the Editorial Board will consider short contributions which should not exceed five typewritten pages. Four types of communication will be considered in this category.**
   (a) **Ideas relating to cancer treatment.**
   (b) **Preliminary research reports.**
   (c) **Clinical case reports.**
   (d) **Brief clinical trials of novel treatments.**

All material submitted for consideration in the journal will be subject to review when appropriate by at least two outside reviewers and one member of the Editorial Board. The decision to publish a manuscript is solely the responsibility of the Editorial Board.

The second part of this journal will consist of supplements which may include proceedings of meetings and symposia and program information from the Division of Cancer Treatment, National Cancer Institute. Requests to publish information in *Cancer Treatment Reports* supplement will be considered by the Editorial Board.

Subscriptions

Cancer Treatment Reports is for sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402. The yearly subscription rate is $38.35 domestic, with an additional $9.60 for foreign mailing. The prices vary for individual issues. Payment is required in advance; check or money order should be made payable to the Superintendent of Documents. Please specify List ID "CAN" (the identifying code for this journal) when requesting a subscription.

INSTRUCTIONS TO AUTHORS

Summary
Begin the article with a short summary.

Text
Submit an original and three copies of the manuscript, typed double spaced. Each page should begin with a new paragraph. Use accepted spelling, abbreviation, and hyphenation found in *Webster's New International Dictionary*. Footnotes should be typed at the bottom of the page on which they appear.

Tables
Submit each table on a separate page, typed double spaced. Please use standard abbreviations; otherwise spell out.

References
Submit references typed double spaced. Follow the standard form of *Index Medicus:* author, title, name of journal, volume number, page or inclusive pages, and year. In book references give author, title of book, edition (if more than one), city and name of publisher, date of book, volume number, and pages cited. References in text should begin with number 1 and continue consecutively. References to papers presented at meetings should include author; title of paper; title, city, and date of meeting; city and name of publisher; date of publication; volume number; and pages. Papers presented at meetings but not published should be cited in a footnote rather than in the reference section.

Illustrations
Photographs and graphs preferably should be clear, glossy prints. Original art work should be done in black ink for good reproduction. Please send 2 copies of each print. Color photographs cannot be used.

Nomenclature
Names of compounds should conform to American usage. See *Chemical Abstracts* for proper nomenclature.

Abbreviations
Only standard abbreviations are acceptable. If a new or coined abbreviation is used, it must be defined when first mentioned.

Brief Reports
Manuscripts published in the Brief Reports section can be no longer than 5 double-spaced pages including references, tables, and a short summary; figures are usually omitted.

Letters to the Editor
Letters to the Editor can be no longer than 3 double-spaced text pages and can be submitted with no more than 1 table and 5 references; figures are usually omitted.

Symposia
Requests to publish the proceedings of symposia should be addressed to the Managing Editor. A copy of the agenda and a list of speakers should accompany such requests.

Submission of Manuscripts
Manuscripts and all inquiries concerning the status of manuscripts should be addressed to: Managing Editor, Cancer Treatment Reports, National Cancer Institute, 8300 Colesville Rd, Rm 3A05, Blair Bldg, Silver Spring, Md 20910. We invite all authors to submit with their manuscripts a short list of possible reviewers. The editorial board will take these names into consideration in selecting those who will be asked to evaluate your manuscript.

Reprints
Supplied free of charge: 250 reprints will be sent to the senior author about three weeks after publication of the article.

Contents

Cancer Treatment Reports
Vol. 62, No. 4
April 1978

Page

ARTICLES

Isophosphamide Therapy for Hematologic Malignancies in Patients Refractory to Prior Treatment 493
Victorio Rodriguez, Kenneth B. McCredie, Michael J. Keating, Manuel Valdivieso, Gerald P. Bodey, and Emil J Freireich
The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston

A Possible New Approach to the Treatment of Metastatic Breast Cancer: Massive Doses of Medroxyprogesterone Acetate 499
F. Pannuti, A. Martoni, G. R. Lenaz, E. Piana, and P. Nanni
M. Malpighi Hospital, Bologna, Italy

Combination Chemotherapy Plus Methanol Extracted Residue of Bacillus Calmette-Guérin or *Corynebacterium parvum* in Stage III Lung Cancer 505
Sigurdur Bjornsson, Hiroshi Takita, Norbert Kuberka, Harvey Preisler, Haya Catane, Donald Higby, and Edward Henderson
Roswell Park Memorial Institute, Buffalo, New York

Intracellular Localization of *meso*-Tetra(*p*-sulfophenyl)porphine: A Potential Tumor Localizing Agent 511
Jack D. Austen, Stewart McConnell, Carl J. Carrano, and Minoru Tsutsui
Texas A and M University, College Station

Studies of the Growth, Population Kinetics, and Host Lethality of $CD8F_1$ Mammary Adenocarcinoma 519
L. Simpson-Herren, D. P. Griswold, Jr, and T. H. Corbett
Southern Research Institute, Birmingham, Alabama

Analysis of Methotrexate and 7-Hydroxymethotrexate by High-Pressure Liquid Chromatography 529
Jeffrey L. Wisnicki, William P. Tong, and David B. Ludlum
Albany Medical College, New York

Qualitative and Quantitative Toxicity of Single and Sequential Sublethal Doses of 5-Fluorouracil in BDF_1 Mice 533
S. D. Harrison, Jr, E. P. Denine, and J. C. Peckham
Southern Research Institute, Birmingham, Alabama

Page

BRIEF REPORTS AND PRELIMINARY COMMUNICATIONS

Influence of Continuous Infusion of Cytosine Arabinoside on Sequencing With Daunorubicin in L1210 Leukemia 547
Mark Edelstein, Fred Valeriote, and Teresa Vietti
Washington University School of Medicine, St. Louis, Missouri

Phase II Study of Mitomycin C, Cyclophosphamide, and Methotrexate in Drug-Resistant Colorectal Carcinoma 549
Cary A. Presant, Gary Ratkin, and Carol Klahr
The Jewish Hospital of St. Louis, Washington University School of Medicine, Missouri

Recurrent Bladder Papillomata Treated With Bacillus Calmette-Guérin: A Preliminary Report (Phase I Trial) 551
Y. Douville, G. Pelouze, R. Roy, R. Charrois, A. Kibrité, M. Martin, L. Dionne, L. Coulonval, and J. Robinson
General Surgery Service, L'Hôtel-Dieu de Québec, Canada

Phase II Study of Baker's Antifol in Advanced Colorectal Cancer 553
Fernando Padilla, Juan Correa, Thomas Buroker, and Vainutis K. Vaitkevicius
Gastrointestinal Committee of the Southwest Oncology Group

Treatment of Advanced Ovarian Cancer With *cis*-Dichlorodiammineplatinum(II): Poor-Risk Patients With Intensive Prior Therapy 555
Howard W. Bruckner, Carmel J. Cohen, Robert C. Wallach, Bernard Kabakow, Gunter Deppe, Ezra M. Greenspan, Saul B. Gusberg, and James F. Holland
Mt. Sinai School of Medicine, New York, New York

***cis*-Dichlorodiammineplatinum(II) as Third-Line Chemotherapy in Advanced Ovarian Adenocarcinoma** 559
M. Steven Piver, Joseph J. Barlow, Shashikant B. Lele, and Donald J. Higby
Roswell Park Memorial Institute, Buffalo, New York

Ataxia and Athetosis as Side Effects of Chemotherapy With Vincristine in Non-Hodgkin's Lymphoma 561
Ugo Carpentieri and Lillian H. Lockhart
University of Texas Medical Branch, Galveston

Phase II Trial of 5-Fluorouracil, Adriamycin, and Mitomycin C in Advanced Colorectal Cancer 563
Daniel G. Haller, Paul V. Woolley, John S. Macdonald, Lee F. Smith, Jr, and Philip S. Schein
Vincent T. Lombardi Cancer Research Center, Georgetown University School of Medicine, Washington, DC

Page

LETTERS

Hexamethylmelamine, Bleomycin, and CCNU Chemotherapy for Patients With Squamous Cell Carcinoma, Large Cell Carcinoma, and Adenocarcinoma of the Lung Unresponsive to Cyclophosphamide, Adriamycin, Methotrexate, and Procarbazine 567
Uri Mintz, Jacob D. Bitran, Judith A. Cooksey, Richard K. Desser, Tom R. DeMeester, and Harvey M. Golomb
University of Chicago Hospitals and Clinics, Illinois

Raynaud's Phenomenon After Vinblastine-Bleomycin Chemotherapy 569
Harvey Rothberg
Princeton Medical Center, New Jersey

Chronic Bleomycin-Associated Raynaud's Phenomenon 570
Allen R. Soble
Oakland Internists Associates, Southfield, Michigan

Raynaud's Phenomenon After Bleomycin Treatment 570
D. P. Chernicoff, R. M. Bukowski, and J. R. Young
The Cleveland Clinic, Ohio

Malignant Melanoma (Stage IIIB): A Pilot Study of Adjuvant Chemo-Immunotherapy 571
Alexander H. G. Paterson, T. Alexander McPherson, and D. J. Willans
Dr. W. W. Cross Cancer Institute, Edmonton, Alberta, Canada

Systemic Epithelioid Granulomata Following Immunotherapy With Methanol Extracted Residue of Bacillus Calmette-Guérin 573
Ira S. Jaffrey
Bardonia, New York

Rhabdomyolysis as a Complication of 5-Azacytidine 573
H. Phillip Koeffler and Charles M. Haskell
University of California School of Medicine, Los Angeles

Gynecomastia With Nitrosourea Therapy 574
Anna E. Schorer, Martin M. Oken, and Gerhard J. Johnson
Veterans' Administration Hospital and University of Minnesota, Minneapolis

Inactivity of DL-Amygdalin Against Human Breast and Colon Tumor Xenografts in Athymic (Nude) Mice 576
Artemio A. Ovejera, David P. Houchens, Anna D. Barker, and John M. Venditti
Battelle Memorial Institute, Columbus, Ohio

Page

Cumulative Indexes: *Cancer Chemotherapy Reports* (1966–1975)

Subject Index

Part 1 579
Part 2 629
Part 3 637

Author Index

Part 1 649
Part 2 665
Part 3 667

ANNOUNCEMENTS 671

Conference on "Combined Modalities: Chemotherapy/Radiotherapy"
Monograph on Non-Hodgkin's Lymphoma
Seminars in Oncology at Roswell Park Memorial Institute
Third Annual "Symposium on Advances in Cancer Treatment Research"
23rd Annual Clinical Conference on "Cancer of the Genitourinary Tract"

The Secretary of Health, Education, and Welfare has determined that the publication of this periodical is necessary in the transaction of the public business required by law of this Department. Use of funds for printing this periodical has been approved by the Director of the Office of Management and Budget through January 31, 1980.

Isophosphamide Therapy for Hematologic Malignancies in Patients Refractory to Prior Treatment [1,2]

Victorio Rodriguez,* Kenneth B. McCredie, Michael J. Keating, Manuel Valdivieso, Gerald P. Bodey, and Emil J Freireich [3]

SUMMARY

Isophosphamide was administered to 27 patients with acute leukemia and to 15 patients with malignant lymphoma refractory to primary therapy. The starting dose of isophosphamide was 1200 mg/m² administered as a daily continuous infusion × 5 days; the courses of treatment were repeated every 2–3 weeks. Of the 27 patients with acute leukemia, four achieved complete remission, two achieved partial remission, and two achieved hematologic improvement. However, no responses occurred in ten patients with acute myelogenous leukemia (AML). Thus, the response rate was 47% (eight responses among 17 patients) in patients with acute lymphoblastic leukemia and acute undifferentiated leukemia. Seven of the 15 patients with malignant lymphoma responded. Most responses (five of six patients) occurred in patients with diffuse histiocytic lymphoma. Twenty-one of the 42 patients had received prior therapy with cyclophosphamide and 12 of these patients (two with leukemia and ten with lymphoma) responded, thus suggesting that as in the treatment of L1210 leukemia, isophosphamide is effective for tumors resistant to prior cyclophosphamide therapy. No significant genitourinary toxicity occurred; however, myelosuppression became the dose-limiting toxicity. Isophosphamide is active in malignant lymphomas and acute leukemias (except AML) and may have a role in combination regimens for such diseases.

[Cancer Treat Rep 62:493–497, 1978]

Isophosphamide, an analog of cyclophosphamide, is an alkylating agent with antitumor activity in L1210 leukemia, Lewis lung carcinoma, Yoshida ascites sarcoma, solid Yoshida sarcoma, Walker 256 carcinosarcoma, TA nephroblastoma, and the chemotherapy-resistant DS carcinosarcoma. Isophosphamide is also of clinical interest because it appears to be effective against a cyclophosphamide-resistant L1210 leukemia (1). Initial clinical trials have demonstrated that isophosphamide has antitumor activity in patients with carcinoma of the lung and gastrointestinal and genitourinary cancers. However, no extensive clinical experience in treating hematologic malignancies has been reported. The toxicity of isophosphamide in patients is similar to that of cyclophosphamide. However, the drug's dose-limiting toxicity is mainly on the genitourinary system, when it has been used in large single doses administered by rapid iv infusion (2–4). We conducted a phase I study of isophosphamide using dose fractionation in an attempt to reduce toxicity while preserving the drug's antitumor effect. The study indicated that the toxicity of isophosphamide could be substantially reduced if the drug was administered daily × 5 days by an iv infusion of 1–2 hours (5). During that study, responses were seen in various patients with solid tumors, in two of two patients with malignant

[1]Received Oct 7, 1977; revised Jan 10, 1978; accepted Jan 26, 1978.

[2]Supported in part by Public Health Service grants CA-05831 and CA-11520 from the National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare; and a grant-in-aid from the Mead Johnson Research Center, Evansville, Ind.

[3]Department of Developmental Therapeutics, The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston.

**Reprint requests to:* Victorio Rodriguez, MD, Southwest Oncology Associates, PA, 7430 Louis Pasteur Dr, San Antonio, Tex 78229.

lymphoma, and in one of 11 patients with acute leukemia refractory to prior therapy. These preliminary results encouraged us to conduct a phase II study of isophosphamide in hematologic malignancies. The main objective of this study was to investigate the therapeutic efficacy of isophosphamide in patients with malignant lymphoma and acute leukemia refractory to prior therapy, and to further attempt a decrease in the genitourinary toxicity from this drug by administering the courses of treatment by daily continuous infusion × 5 days.

MATERIALS AND METHODS

All patients with histologic proof of acute leukemia or advanced malignant lymphoma who had failed prior remission induction therapy were eligible for this study. Patients entered in the study had not received previous chemotherapy or radiotherapy for ≥ 2 weeks and had recovered from the toxic effects of prior therapy. Isophosphamide was administered as a daily continuous infusion × 5 days; the initial dose was 1200 mg/m²/day × 5 days. Each daily dose of drug was given in 2000–3000 ml of dextrose solution. Courses of therapy were repeated every 2–3 weeks depending on the recovery from myelosuppression or other toxicity. The dose was escalated in subsequent courses of therapy if no changes were seen in the patient's bone marrow (leukemia patients) or if myelosuppression was tolerable (malignant lymphoma patients). The dose escalations were 1500 and 1800 mg/m²/day × 5 days for courses two and three respectively. The drug dose was decreased by 25% if the patients developed new microscopic hematuria during the preceding course or if they had profound myelosuppression. Therapy was discontinued if any patient developed clinically apparent severe dysuria or hemorrhagic cystitis. Prior to entering the study, all patients had a complete history and physical examination; an extensive documentation of the disease was made. Cbc, differential, and platelet counts, urinalysis, BUN, creatinine, liver function tests, and a pretreatment bone marrow aspiration and biopsy were taken. During the study, patients were followed with serial cbc, differential, and platelet counts, weekly SMA–100, and daily urinalysis during the 5 days of chemotherapy as well as weekly thereafter. A bone marrow examination was repeated before each course of therapy in most patients with acute leukemia and in those patients with lymphoma involving the bone marrow.

In acute leukemia, a complete remission (CR) was recorded when patients had < 5% leukemic cells in the bone marrow, when the polymorphonuclear counts were > 1000/mm³, when the platelet counts were > 100,000/mm³, and when no clinical evidence of disease was detectable. A partial remission (PR) was recorded when the patient's bone marrow contained 6%–30% blast cells and the peripheral counts became normal as previously described. Hematologic improvement was recorded in patients with acute leukemia in whom the blood count temporarily returned to normal levels, but in whom the marrow did not achieve at least a PR status. In patients with malignant lymphoma, CR was defined as the disappearance of all evidence of disease and the return of clinical well-being. PR was defined as a > 50% reduction of the sum of two diameters in all tumor masses. Stabilization of disease was defined as < 50% regression of the tumor. Patients received, if possible, three courses of chemotherapy before they were considered to have failed; however, those patients in whom the disease was progressing very rapidly after the first or second course were removed from the study if there was no evidence of some improvement. Duration of remission was measured from the time the response occurred. Survival was measured from the start of therapy.

RESULTS

Twenty-seven patients with acute leukemia and 15 with malignant lymphoma were entered in this study. All patients had received prior therapy and were refractory to it. Of the 27 patients with acute leukemia, 16 were males and 11 were females; they had an age range of 15–59 years (median age, 27 years). Most patients had acute lymphoblastic leukemia (ALL) or acute undifferentiated leukemia (AUL); only ten had acute myelogenous leukemia (AML). All patients had had prior extensive chemotherapy with various regimens, mainly combinations of adriamycin and cytosine arabinoside (Ad-OAP) (6). However, in seven patients, prior therapy consisted of a combination of cyclophosphamide, vincristine, cytosine arabinoside, and prednisone (COAP).

The response of the patients with acute leukemia receiving isophosphamide is shown in table 1. Five patients who died of rapidly progressing disease within the first week of therapy were considered early deaths. Two patients who received only one course of therapy and died within the second week after initiation of therapy were considered to have received inadequate trials. Of all 27 patients entered, four achieved CR, two achieved PR, two had hematologic improvement, and 14 failed to respond. However, if only patients who received adequate trials were considered, 20% achieved a CR and 10%

TABLE 1.—Acute leukemia: responses with isophosphamide

Type of leukemia	No. of patients entered	No. of patients with—				
		Early death	CR	PR	Hematologic improvement	No. of failures
ALL	12	1	4	1	1	5
AML	10	3	—	—	—	7
AUL	5	1	—	1	1	2
Totals	27	5	4	2	2	14

TABLE 2.—Response and prior therapy in patients with ALL and AUL

Type of prior therapy	No. of patients entered	No. of patients with—			
		CR	PR	Hematologic improvement	No. of failures
Cyclophosphamide	6	—	1	1	4
Other agents*	9	4	1	1	3

*Cytosine arabinoside, adriamycin, 5-azacytidine, 6-mercaptopurine, methotrexate, vincristine, prednisone.

achieved a PR, for an overall response rate of 30%. Table 1 also shows the response according to histologic type of leukemia. No responses occurred among the ten patients with AML. The four CRs and one of the two PRs occurred in the 12 patients with ALL, for an overall response rate of 42%.

The response of the patients with ALL and AUL was analyzed in relation to prior chemotherapy as shown in table 2. Those six patients who had received prior combination therapy with COAP are listed as having received cyclophosphamide in the table. The remaining patients received various other combinations of cytosine arabinoside, adriamycin, methotrexate, 6-mercaptopurine, vincristine, and prednisone (6). The four patients who achieved CR, one who achieved PR, and one who achieved hematologic improvement were among those who did not receive cyclophosphamide as prior therapy. Among the patients receiving the COAP regimen previously, only one achieved PR and one had hematologic improvement.

The median duration of CR in the four patients responding in this study was 17 weeks (range, 8–26); the duration of PR in the two patients responding was 5 and 11 weeks respectively.

The results in 15 patients with malignant lymphoma were also analyzed. Eight patients were men and seven were women; the median age was 46 with a range of 22–72. The majority of patients had diffuse histiocytic lymphoma or nodular poorly differentiated lymphoma. Two patients had well-differentiated lymphocytic lymphoma with blood and bone marrow involvement, and therefore may be considered as having chronic lymphocytic leukemia. All patients had become refractory to prior therapy with a combination of cyclophosphamide, adriamycin, vincristine, and prednisone (7).

No CRs were observed in this group of patients with malignant lymphoma (table 3); however, seven of the 15 patients achieved a PR and three achieved stabilization of disease (< 50% response). The majority of responses occurred in patients with diffuse histiocytic lymphoma (five of six patients). Of six patients with nodular poorly differentiated lymphoma, only one responded and three achieved stabilization of disease. No responses were seen in the two patients with chronic lymphocytic leukemia. The only patient with diffuse poorly differentiated lymphocytic lymphoma achieved a PR. The duration of response in patients with malignant lymphoma ranged from 4 to 20 weeks, with a median of 6 weeks.

The toxicity of isophosphamide in these patients was mainly to the bone marrow (table 4). Of the 27 patients with acute leukemia, 19 developed significant myelosuppression. The median lowest blood cell counts are shown in the table. Twelve of the 15 patients with malignant lymphoma developed myelosuppression; the lowest wbc and platelet counts were twice those of patients with acute leukemia.

TABLE 3.—Malignant lymphoma: response with isophosphamide*

Type of lymphoma†	No. of patients entered	No. of patients with— PR	Stable disease	No. of failures
DWDL	2	—	—	2
DPDL	1	1	—	—
DH	6	5	—	1
NPDL	6	1	3	2
Totals	15	7	3	5

*All patients had received prior therapy with cyclophosphamide.
†DWDL = diffuse well-differentiated lymphocytic (chronic lymphocytic leukemia); DPDL = diffuse poorly differentiated lymphocytic; DH = diffuse histiocytic; NPDL = nodular poorly differentiated lymphocytic.

TABLE 4.—Myelosuppression with isophosphamide

Disease	Median (range) Lowest wbc count ($\times 10^3$ cells/mm^3)	Day	Median (range) Lowest platelet count ($\times 10^3$ cells/mm^3)	Day
Leukemia	0.7(0.1–2.4)	10(4–14)	32(3–137)	8(5–18)
Lymphoma	1.7(0.5–3.0)	13(8–16)	71(6–134)	13(7–19)

Genitourinary toxicity occurred in six patients with acute leukemia and in eight patients with lymphoma; this consisted mainly of microscopic hematuria. However, in six patients, macroscopic hematuria (hemorrhagic cystitis) was evident. Nine of the 42 patients experienced various other side effects: nausea (four patients), drowsiness and hyponatremia (two patients), or infection during myelosuppression (three patients). No other major side effects were seen with this regimen. The continuous infusion administration of isophosphamide was relatively well-tolerated by most patients and no local phlebitis or abnormalities of liver function could be detected that might be attributable to isophosphamide. None of our patients received bladder catheterization or any other instrumentation to decrease the genitourinary toxicity.

DISCUSSION

This study indicates that isophosphamide is a chemotherapeutic agent of clinical efficacy in patients with hematologic malignancies. Our study was performed in patients who had received prior primary therapy and were refractory to other first-line agents. Therefore, the patients in this study represent a selected population. Few other efficacious agents were readily available. Therefore, the clinical improvements found in this study, which indicate efficacy of isophosphamide, were important.

The overall CR and PR rate in the patients with acute leukemia in this study was 22%; however, if the five early deaths are excluded, the overall response rate is 27%. Furthermore, since no responses were seen in AML, it might be inferred that the response rate in the population expected to be responsive to isophosphamide is 35% (six of 17 patients). During our phase I study with isophosphamide, one of 11 patients with AML treated with similar doses responded (5). In this study, there were no responses in patients with AML. Therefore, it appears safe to conclude that the efficacy of isophosphamide in AML, if present, is negligible.

Responses in acute leukemia were more frequent in those patients who had not received cyclophosphamide prior to isophosphamide therapy, although two responses were also seen among patients receiving prior cyclophosphamide. All the responses in malignant lymphoma occurred in patients who had received prior therapy with cyclophosphamide. This suggests that, as in L1210, isophosphamide might have efficacy in patients treated with prior alkylating agents.

Our experience in patients with malignant lymphoma, although not very extensive, is quite en-

couraging. Although there were no CRs in this population of patients, seven PRs occurred in 15 patients. Most important is the observation that five of the seven PRs occurred among patients with diffuse histiocytic lymphoma. These patients had advanced disease and had progressed on other regimens. The responses in these patients with malignant lymphoma are also encouraging from the point of view of their prior therapy and tend to confirm the experimental data on L1210 leukemia.

The drug was very well-tolerated; myelosuppression was the dose-limiting toxicity. Myelosuppression was more pronounced in patients with leukemia than in patients with lymphoma. Genitourinary toxicity, manifested as microscopic and occasionally as macroscopic hematuria, was seen in only a few patients. This is similar to the experience that we had reported previously in our phase I study (5). No evidence of azotemia or liver dysfunction attributable to the drug was seen during this study. However, two patients developed confusion and electrolyte imbalance that might have been attributed to isophosphamide. Other investigators have reported similar findings in patients receiving this drug (2).

Our favorable results in hematologic malignancies might be due to the method of administration of the drug. Other investigators who have used single high doses have not seen important responses in hematologic malignancies. We decided to use fractionated doses and administer the drug by continuous infusion. The pharmacology of fractionated administration of isophosphamide indicates that the proportion of drug metabolized is larger and amounts of unchanged drug excreted in the urine are smaller than after single large doses (8). This might have been responsible for the favorable results that we observed in our studies. Although the therapeutic results were improved, the side effects were not accentuated, except for myelosuppression which became dose-limiting toxicity. Other side effects were substantially fewer than the number of side effects reported in the literature by other groups (2–4).

Whether the administration of isophosphamide daily × 5 days in infusions of 1–2 hours, which we used initially (5), or the administration over 5 days by continuous infusion, as used in the present study, is better cannot be ascertained from the study. Nevertheless, the method of fractionated administration has resulted in improved therapeutic efficacy and decreased toxicity. Our studies indicate that isophosphamide is active and that this drug may have a role in the initial combination regimens for some hematologic malignancies.

REFERENCES

1. BROCK N. Pharmacological studies with ifosfamide—a new oxazaphosphorine compound (Proceedings of the 7th International Congress of Chemotherapy, Prague, 1971). *In* Advances in Antimicrobial and Antineoplastic Chemotherapy (Semonský M, Hejzler M, and Masák S, eds). Baltimore, University Park Press, vol 2, 1972, pp 749–756.
2. BREMNER DN, MCCORMICK JStC, and THOMSON JWW. Clinical trial of isophosphamide (NSC-109724)—results and side effects. Cancer Chemother Rep 58:889–893, 1975.
3. COHEN MH, CREAVEN PJ, TEJADA F, ET AL. Phase I clinical trial of isophosphamide (NSC-109724). Cancer Chemother Rep 59:751–755, 1975.
4. SCHEEF W. Problems, experience and results of clinical investigations with ifosfamide (Proceedings of the 7th International Congress of Chemotherapy, Prague, 1971). *In* Advances in Antimicrobial and Antineoplastic Chemotherapy (Semonský M, Hejzler M, and Masák S, eds). Baltimore, University Park Press, vol 2, 1972, pp 797–800.
5. RODRIGUEZ V, BODEY GP, FREIREICH EJ, ET AL. Reduction of ifosfamide toxicity using dose fractionation. Cancer Res 36:2945–2948, 1976.
6. BODEY GP, COLTMAN CA, HEWLETT JS, ET AL. Progress in the treatment of adults with acute leukemia. Review of regimens containing cytarabine studied by the Southwest Oncology Group. Arch Intern Med 136:1383–1388, 1976.
7. MCKELVEY EM, GOTTLIEB JA, WILSON HE, ET AL. Hydroxyldaunomycin (adriamycin) combination chemotherapy in malignant lymphoma. Cancer 38:1484–1493, 1976.
8. NELSON RL, ALLEN LM, and CREAVEN PJ. Pharmacokinetics of divided dose ifosfamide. Clin Pharmacol Ther 19:365–370, 1976.

A Possible New Approach to the Treatment of Metastatic Breast Cancer: Massive Doses of Medroxyprogesterone Acetate [1]

F. Pannuti,* A. Martoni, G. R. Lenaz, E. Piana, and P. Nanni [2,3]

SUMMARY

The results obtained with a new hormone therapy using medroxyprogesterone acetate (MAP) in previously untested single and total doses in the treatment of advanced breast cancer are reported. Fifty-two postmenopausal patients were treated with an average total dose of 40 g of MAP for a period of 30 days. Nineteen of 44 patients (43%) had complete or partial remission, while the disease remained unchanged in nine of 44 patients (20%). Disease progression occurred in 12 of 44 patients (27%). Partial or complete remission occurred in 12 of 18 (67%) and four of six (67%) of the patients with dominant osseous and soft tissue metastases respectively. Three of ten (16%) of those with visceral metastases had remission. The average duration of remission was 7 months. Average survival times were 15.5 months for patients with remission, 8 months for those with no change, and 2.5 months for those with disease progression. From a subjective standpoint, pain was reduced significantly or disappeared in 34 of 36 patients (94%); this was also the case with respect to dyspnea (13 of 16 patients [81%]), anorexia (24 of 29 [83%]), asthenia (28 of 35 [80%]), and walking impairment (15 of 24 [63%]). When relapse occurred, patients previously treated with massive doses of MAP received further treatment with higher doses of MAP; four of 22 (18%) of the patients attained partial remission once again. Positive effects were also seen in subjective performance status, body weight, and EKG. We also describe the new clinical and toxicologic features of this treatment.

[Cancer Treat Rep 62:499–504, 1978]

Medroxyprogesterone acetate (MAP) is a semisynthetic progestogen possessing high progestational activity and causing strong pituitary inhibition (1); it has been used for some time in the treatment of advanced breast cancer (2). In 1964 the Cooperative Breast Cancer Group reported objective remission in six of 24 patients (25%) treated with a regimen using an oral dose of 266 mg/day of MAP (3). Subsequent clinical trials with oral doses of 100 mg/day failed to confirm these results and the drug appeared to be almost completely without effect (4,5). Klaassen et al (6) have recently treated a group of patients with 200–300 mg of oral or im MAP, obtaining two partial remissions among 40 patients (5%). It has been pointed out by all investigators that low doses of MAP do not produce any significant side effects.

In October 1972 we began a study aimed at: (*a*) establishing the single and total maximum tolerated doses of MAP; (*b*) establishing the remission rate and duration of treatment obtained with these doses; and (*c*) establishing the effect of a second cycle of MAP treatment at massive doses used after the appearance of relapse. The results relating to (*a*) have already been reported elsewhere (7). In a preliminary study in a group of 17 patients with advanced breast cancer, the highest daily im dose of MAP that was tolerated was 1500 mg, while the mean total dose was 40 g. Higher single or total doses could not be used for reasons of local tolerance. The same MAP treatment was subsequently

[1] Received Mar 9, 1976; revised Oct 17, 1977; accepted Jan 17, 1978.

[2] Division of Oncology, M. Malpighi Hospital, Bologna, Italy.

[3] We are grateful to the *Cancer Treatment Reports* editorial staff for their helpful advice and criticism in the preparation of this manuscript.

Reprint requests to: Prof. Franco Pannuti, Divisione di Chemioterapia, Ospedale Provinciale Specializzato M. Malpighi, Via Albertoni N. 15, Bologna 40138, Italy.

TABLE 1.—Clinical characteristics (52 patients)

Characteristic	Median	Range
Age (yrs)	58	37–81
Time from menopause (mos)	108	2–444
Disease-free interval (mos)	19	1–108
MAP total dose (g)	40	19.5–70*
Days of treatment	26	13–47
	No. of patients	
Dominant site of lesions		
Soft tissue	6	
Osseous	22	
Visceral	24	
Previous treatment		
Radical mastectomy	46	
Primary radiotherapy	3	
Postoperative radiotherapy	37	
Surgery for relapse	10	
Palliative radiotherapy	26	
Castration	11	
Hypophysectomy	3	
Androgens	14	
Estrogens	1	
Progestogens	3	
Chemotherapy	13	
No previous treatment	2†	

*Only 3 patients received > 50 g.
†$T_{4c}N_2M_1$ and $T_{4c}N_1M_1$.

adopted for other patients with advanced breast cancer. The present report reviews the overall results obtained from treatment of the first 52 patients.

MATERIALS AND METHODS

We administered MAP at a daily dose of 1500 mg by gluteal im injection, subdivided into two equal doses at 12-hour intervals, to 52 consecutive postmenopausal patients with advanced histologically proven breast cancer (first treatment). The features of the patient group are described in table 1. Duration of treatment was limited to 1 month, since after this period the injection area displays intolerance, making it no longer possible to give treatment in the majority of cases.

After completion of such treatment no maintenance therapy was carried out in order to assess possible long-term toxic effects. In light of this, a further 1-month period of intensive therapy was begun on the appearance of relapse exclusively in those patients who had shown minimal (MR), partial (PR), or complete (CR) remission or had remained unchanged (NC) after the first period of treatment. During the second treatment the daily im dose given was 1500 mg in the first four patients and 2000 mg in the remaining 19 patients. These daily doses were split into two equal injections with a 12-hour interval between them. The 2000-mg/day dose was also administered over a period of 30 days for two reasons: (*a*) the concentration of MAP in the pharmaceutic compound that was available later in the study was higher than the concentration of the compound we were testing at the beginning of our experiments; and (*b*) the side effects encountered in a further group of patients who had never been previously treated with this new preparation at 2000-mg/day doses did not differ from those resulting from a daily 1500-mg dose given over a period of 30 days (8).

All patients had a life expectancy of at least 2 months and none of them had undergone any kind of antitumor treatment for at least 1 month; their performance status, based on the Karnofsky scale (9), was > 30% and the disease was in progression. Patients receiving a total dose of at least 15 g were evaluated for remission. Evaluation of remission was performed within 6 months from the beginning of the treatment. The evaluation criteria adopted were as follows: *CR*—complete disappearance of all lesions for at least 6 months; *PR*—a 50% decrease in the surface area of all measurable lesions and thickening or no change in osseous lesions for at least 3 months together with remission of pain; *MR*—a decrease in the surface area of all measurable lesions ranging between 25% and 50% and CR or PR of some lesions with no change in the remainder for at least 1 month; *NC*—no appreciable change or < 25% decrease in measurable lesions; *progression*—a 25% increase in at least one measurable lesion, occurrence of new lesions, or progression of osteolytic metastases; *relapse*—appearance of new lesions or 25% increase in surface area of all measurable lesions following a period of remission or NC.

Before and after treatment all patients received the usual hematologic tests (wbcs, rbcs, hemoglobin, platelets, erythrocyte sedimentation rate, total protein, bilirubin, prothrombin clotting time, BSP, SGOT, SGPT, total cholesterol, acid and alkaline phosphatase, glucose, BUN, creatinine, uric acid, sodium, potassium, calcium, and phosphorus in plasma and urine, and urinalysis), EKG, roentgenographic evaluation (thorax, cranium, and pelvis), liver scan, and clinical evaluation. After treatment all patients were submitted to monthly clinical and, if needed, roentgenographic evaluation.

All other therapy was omitted during and after MAP treatment to avoid possible antitumor effects and/or possible drug interference. In patients with severe pain we administered pentazocine, and two patients with hypertension received clonidine.

TABLE 2.—Toxic effects of MAP treatment

Side effects	No. of patients with effect/No. evaluated	
	1st treatment	2nd treatment
Gluteal abscess	17/52(33%)	5/23(22%)
Gluteal infiltration	0/52	4/23(17%)
Vaginal spotting	5/52(10%)	—
Thrombophlebitis	1/52(2%)	1/23(4%)
Moon facies	13/52(25%)	6/18(33%)
Fine tremors	11/52(21%)	—
Increased sweating	12/52(23%)	4/23(17%)
Muscular cramps	2/52(4%)	1/23(4%)

Hematochemical tests

	Average			Average		
	Before	After	SE	Before	After	SE
Wbcs × 10^3/mm^3	6.352	8.712*	0.044	6.238	7.715‡	0.554
Platelets × 10^3/mm^3	197.854	238.395†	11.127	No significant change		
BUN (mg/100 ml)	32.375	38.035*	1.492	No significant change		
Plasma potassium (mEq/liter)	4.396	4.811*	0.063	4.467	4.846†	0.109
Urinary potassium (mEq/24 hrs)	No significant change			38.470	37.775†	2.898
Urinary sodium (mEq/24 hrs)	120.369	145.845‡	12.035	79.995	111.465†	0.109
Uric acid (mg/100 ml)	5.836	5.178‡	0.277	No significant change		
SGOT (mU/ml)	20.938	14.693‡	2.642	No significant change		
α2-globulins (g/100 ml)	1.428	1.811†	0.810	0.952	1.221†	0.030
Total albumin (g/100 ml)	No significant change			3.712	3.185†	0.134
Total globulin (g/100 ml)	No significant change			3.338	3.771†	0.144

*$P < 0.001$.
†$P < 0.01$.
‡$P < 0.05$.

RESULTS (First Treatment)

Toxicity

In ten patients, treatment was discontinued at lower doses than originally planned; this was due to gluteal abscess in five patients, moderate hyperbilirubinemia in two patients (this condition disappeared 8–10 days after treatment was suspended), and on request of the patient in another two patients. One patient died during treatment from thrombosis of the superior mesenteric artery accompanied by intestinal infarction (multiple liver metastases were found in this instance).

The clinical and hematochemical side effects that followed treatment are listed in table 2, which also compares the toxicity of the first treatment with that of the second treatment. "Moon facies," accompanied by an increase of adipose tissue in the abdominal and cervicodorsal regions, was seen in 13 of 52 patients (25%) after treatment. Neither masculinization nor edema appeared. Fifteen of the 42 patients (36%) treated with a commercial preparation having a concentration of 50 mg/ml showed gluteal abscess. One of ten patients treated with the trial preparation (F.I. 7401, Farmitalia, 200 mg/ml concentration) showed abscess.

After treatment, platelet, wbc, BUN, plasma potassium, and urinary sodium values increased significantly; although uric acid and SGOT values dropped noticeably compared to baseline levels, they remained within the range of normal values (table 2). Statistically significant changes were also seen in α2-globulins (table 2). No significant changes in hemoglobin, bilirubin, BSP, erythrocyte sedimentation rate, SGPT, alkaline phosphatase, calcium, plasma phosphorus, total proteins, cholesterol, glucose, and creatinine were observed. No hypercalcemia was caused by the treatment in any patient. In 23 patients arterial pressure remained unchanged immediately after treatment. Three months after treatment both the diastolic value (average, 88.26–99.60 mm Hg; SE ± 2.96, $P < 0.001$) and the systolic value (average, 150.434–169.13 mm Hg; SE ± 8.31, $P < 0.05$) had increased significantly. After 6 months arterial pressure in the same patients tended to return to baseline values, a significant difference still being found however, in the diastolic values (average 98.69 mm Hg compared to 88.26 mm Hg; SE ± 3.625, $P < 0.01$). No significant changes in the EKG resulted from MAP therapy as has been described elsewhere (10).

TABLE 3.—Response by dominant site of lesions (1st treatment)

Response	No. of patients responding/No. treated			
	Soft tissue	Osseous	Visceral	Total
CR + PR	4/6(67%)	12/18(67%)	3/20(15%)	19/44(43%)
MR	1/6(17%)	0/18	3/20(15%)	4/44(9%)
NC	0/6	4/18(22%)	5/20(25%)	9/44(20%)
Progression	1/6(17%)	2/18(11%)	9/20(45%)	12/44(27%)

Pharmacodynamics

Eight of the 52 patients could not be evaluated; two showed pleural effusion with no other lesions, three were subsequently admitted to other institutions for further cytotoxic treatment in the absence of progression, and we were unable to followup three patients. Of the 44 evaluated patients, one (2%) had CR, 18 (41%) had PR, four (9%) had MR, nine (20%) had NC, and 12 (27%) had progression of disease.

Remission began to occur upon completion of the treatment, particularly with regard to skin lesions and pleural effusion; in all patients, it occurred within 2 months from the end of the treatment. The average duration of remission was 7 months (range, 4.5–24 months).

Table 3 shows the response by site of dominant lesions. The highest remission rate was observed in the group with dominant bone and soft tissue lesions, 12 of 18 (67%) and four of six (67%) respectively. Only one of the five patients who had undergone prophylactic castration achieved PR, whereas five of the six who had undergone therapeutic castration had PR and one had MR. No remissions were recorded in the three patients previously treated by hypophysectomy. Of the 13 patients who had been treated with androgens, seven had PR and one had MR. Two of the three patients who had previously undergone progestogen therapy at low doses had PR.

Remission occurred in three of three patients with pleural metastases, three of five (60%) with primitive neoplasms, four of eight (50%) with skin metastases, five of 11 (45%) with lymph node metastases, 19 of 33 (57%) with osseous metastases (thickening of osteolytic metastases in ten patients), one of eight (12%) with pulmonary metastases, and one of one with peritoneal metastases. None of the eight patients with liver metastases had objective remission.

Pain connected with osseous metastases was reduced significantly or disappeared completely in 34 of 36 patients (94%). Dyspnea was reduced in 13 of 16 patients (81%), asthenia in 28 of 35 patients (80%), anorexia in 24 of 29 patients (83%), and walking impairment in 15 of 24 patients (62%). Pain diminished rapidly. After 2 weeks of treatment severe pain was reported in two of the 26 patients suffering from this condition before beginning the MAP treatment. Only one patient was unable to walk after treatment compared to 12 before treatment.

Performance status, evaluated at 1 month and at 6 months after treatment, improved considerably (from an average of 49.31% before treatment to an average of 65.00% after 1 month [SE ± 2.08, $P < 0.001$] and an average of 73.10% after 6 months [SE ± 2.69, $P < 0.001$]). No changes were found in body weight 1 month after beginning the treatment. Body weight increased significantly from an average of 64.303 kg to an average of 67.603 kg (SE ± 0.958, $P < 0.01$) after 3 months and an average of 68.655 kg (SE ± 2.457, $P < 0.001$) after 6 months.

In patients with either CR or PR average survival was 15.5 months, compared to 8 months in patients with MR or NC. Average survival was 2.5 months in patients with disease progression (fig 1).

RESULTS (Second Treatment)

Toxicity

Table 2 shows the side effects that arose after the second treatment and the most significant statistical changes in the hematologic parameters. The following hematologic parameters rose significantly though they did not exceed normal limits: wbcs, urinary sodium, plasma potassium, and urinary potassium. A significant decrease of total albumins and a significant increase of total and α2-globulins were seen, ranging from normal to pathologic values.

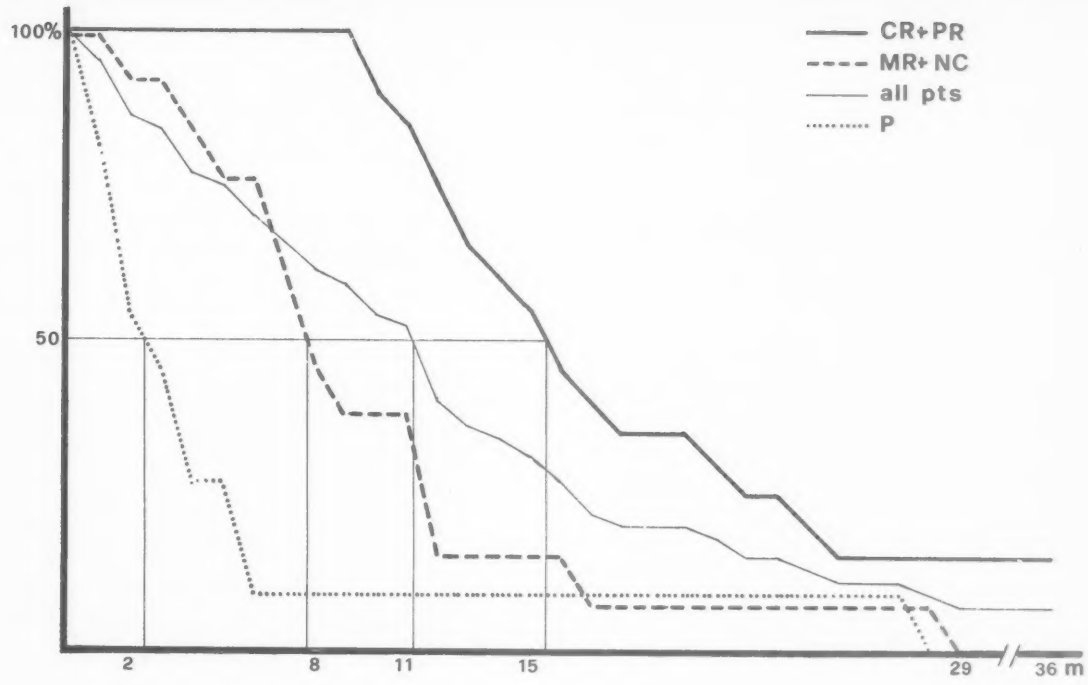


FIGURE 1.—36-mo survival in 52 patients with advanced breast cancer treated with MAP (1500 mg/day × 30 days).

The other hematologic parameters examined did not show any significant modifications. The treatment appeared to cause no hypercalcemia. No alterations were seen in cardiac function, arterial pressure, or EKG.

Pharmacodynamics

There was an average interval of 7 months between the first and the second treatments (range, 2–16 months). One of the 23 patients treated was not assessed because she had only pleural effusion. Four of the remaining 22 patients (18%) had PR, nine (41%) had NC, and eight (36%) had progression of disease. If we compare these results with those obtained after the first treatment (table 4) it can be seen that of the 15 patients who had exhibited PR after the first treatment, four (27%) re-experienced PR, one (7%) attained MR, five (33%) had NC, and another five showed progression of disease. None of the patients with NC after the first treatment showed remission after the second treatment. Significant reduction or disappearance of pain was observed in 20 of 22 patients (91%); improvement was noted in dyspnea in five of 11 patients (45%), asthenia in 11 of 16 (69%), anorexia in six of nine (67%), and walking impairment which was significantly reduced or disappeared in three of nine (33%).

The patients' performance status improved significantly, from 47.407% to 53.333% (SE ± 2.46, $P < 0.05$) after the second treatment, while body weight remained unchanged immediately after the treatment came to an end.

DISCUSSION

No maintenance therapy was carried out after the first MAP cycle because our primary interest was to study the immediate or long-term side effects that might have been caused by this treatment. The drug's toxic profile has never been described before; the main features are a corticoid-like effect (moon facies, considerable increase of appetite, accumulation of fat similar to that recorded for the Cushing syndrome, and a moderate temporary increase in pressure); an antialdosteronic effect (resulting in an increase in the blood potassium and urinary sodium); and an adrenergic-like syndrome (fine hand tremors, diffuse sweating, and brief cramps in the calves at night).

TABLE 4.—Response to the 2nd treatment compared with response to the 1st treatment

1st treatment response	2nd treatment response (No. of patients; total treated = 22)			
	PR	MR	NC	Progression
PR (15 patients)	4(27%)	1(7%)	5(33%)	5(33%)
MR (2 patients)	0	0	0	2
NC (5 patients)	0	0	4	1
Totals	4/22(18%)	1/22(5%)	9/22(41%)	8/22(36%)

Massive doses of MAP induced objective CR or PR in 43% of the patients treated. These results confirm the effect of the progestogen on advanced mammary carcinoma and are also better than those reported by authors using low doses of MAP. We are fully aware that a historical comparison cannot be considered valid even if the cases reviewed by Klaassen (whose patients and evaluation criteria are similar to ours) corroborate our results. Subjective results are of particular interest, especially if we take into account the high percentage of remission of pain due to osseous metastases both during the first and the second treatment.

We were unable to correlate the type of response to massive doses of MAP to the response resulting from previous treatments. This applies particularly to previous hormonal manipulation since we have no reliable information about the actual response of the disease to other treatments; in some cases, these treatments were carried out in institutes that are very far from ours or in non-oncologic hospitals. Furthermore, the information available in these instances refers to a very small number of patients for each category of response, making it impossible to properly compare or statistically evaluate the results.

The incidence of objective PR after the second treatment was much lower (four of 15 patients) than that obtained after induction treatment. Therefore, we believe that the best way to implement maintenance therapy, and the best dose to be used in high-level MAP therapy applied to patients of this kind, remains a subject open to debate. Finally, it can be said that our experience demonstrates that it is possible to use the high doses of MAP in patients with advanced breast cancer. This does not mean that the doses used were necessarily the best that could be tested. On the contrary, it would seem prudent to test lower doses (500–1000 mg/day) in controlled prospective studies in order to gain information on potentially more useful and less costly treatment regimens.

REFERENCES

1. BRIGGS MH, CALDWELL ADS, and PITCHFORD AG. The treatment of cancer by progestogens. Hosp Med 2:63–69, 1967.
2. COOPERATIVE BREAST CANCER GROUP. Progress report: results of studies by the Cooperative Breast Cancer Group—1956–60. Cancer Chemother Rep 11:109–141, 1961.
3. COOPERATIVE BREAST CANCER GROUP. Results of studies of the Cooperative Cancer Group—1961–63. Cancer Chemother Rep (Suppl I) 41:1–24, 1964.
4. SEGALOFF A, CUNINGHAM M, RICE BF, ET AL. Hormonal therapy in cancer of the breast. XXIV. Effect of corticosterone or medroxyprogesterone acetate on clinical course and hormonal excretion. Cancer 20:1673–1678, 1967.
5. GOLDENBERG IS. Clinical trial of Δ^1-testololactone (NSC 23759), medroxy progesterone acetate (NSC 26386) and oxylone acetate (NSC 47438) in advanced female mammary cancer. A report of the Cooperative Breast Cancer Group. Cancer 23:109–112, 1969.
6. KLAASSEN DJ, RAPP EF, and HIRTE WE. Response to medroxyprogesterone acetate (NSC-26386) as secondary hormone therapy for metastatic breast cancer in postmenopausal women. Cancer Treat Rep 60:251–253, 1976.
7. PANNUTI F, MARTONI A, POLLUTRI E, ET AL. Massive-dose progestational therapy in oncology (medroxyprogesterone). Preliminary results. Panminerva Med 18:129–136, 1976.
8. PANNUTI F, MARTONI A, and PIANA E. Higher doses of medroxyprogesterone acetate in the treatment of advanced breast cancer. Int Res Commun Sys Med Sci 5:54, 1977.
9. KARNOFSKY DA, and BURCHENAL JM. The clinical evaluation of chemotherapeutic agents in cancer. *In* Evaluation of Chemotherapeutic Agents (McLeod CM, ed). New York, Columbia University Press, 1949, pp 191–205.
10. PANNUTI F, MARTONI A, POLLUTRI E, ET AL. Massive dose of medroxyprogesterone in oncology: effects on ECG of patients with advanced breast cancer. Boll Soc Ital Biol Sper 50:557–561, 1974.

Combination Chemotherapy Plus Methanol Extracted Residue of Bacillus Calmette-Guérin or *Corynebacterium parvum* in Stage III Lung Cancer [1,2]

Sigurdur Bjornsson,[3,*] Hiroshi Takita,[3] Norbert Kuberka,[4] Harvey Preisler,[3] Haya Catane,[3] Donald Higby,[3] and Edward Henderson[3,5]

SUMMARY

Seventy-six patients with stage III bronchogenic carcinoma were treated with monthly adriamycin, cyclophosphamide, *cis*-dichlorodiammineplatinum(II), and vincristine. In addition, they were randomized to receive either no immunotherapy, the methanol extracted residue of bacillus Calmette-Guérin (MER), or *Corynebacterium parvum* (*C. parvum*). Age, histology, extent of disease, prior therapy, and performance status were comparable in the three treatment groups. Twelve patients (16%) died having received only one treatment cycle. Sixty-four of the 76 patients received two or more treatments and were evaluable for response. There were no patients with complete responses, 14 patients (18%) with partial responses, 28 patients (37%) with no change, and 22 patients (29%) with progressive disease. Survival among patients receiving *C. parvum* is significantly longer ($P < 0.05$) than that of patients receiving either MER or no immunotherapy.

[Cancer Treat Rep 62:505–510, 1978]

Metastatic non-small cell bronchogenic carcinoma is a disease whose fatal outcome has not been altered by antineoplastic chemotherapy (CT). It has been suggested, in fact, that single-agent and combination CT adversely affect both patient survival and quality of remaining life (1). Most investigators agree, however, that combination CT is worthy of trial since useful partial responses (PR) can be achieved in 20%–40% of the patients treated and responding patients will survive longer than nonresponders (2–7). At the Roswell Park Memorial Institute the combination of *cis*-dichlorodiammineplatinum(II) (DDP) and adriamycin (ADM) produced ≥ 50% tumor regression in four of six patients (8). Cyclophosphamide (CTX) has been shown to produce responses in patients with bronchogenic carcinoma when used alone (9) or in combination with ADM (8) or DDP (10). Hence, we decided to evaluate a CT combination which included all three agents. Systemic, nonspecific immunotherapy has shown some promise in lung cancer, both when used alone (11,12) and in combination with CT (13,14). We report here our results using a four-drug combination with or without immunotherapy in advanced lung cancer. We have included two patients with small cell carcinoma who had progressed on previous CT.

MATERIALS AND METHODS

Seventy-six patients with stage III bronchogenic carcinoma at the Roswell Park Memorial Institute and the Millard Fillmore Hospital, Buffalo, NY, were entered in the study from January 1976 to March 1977. There were 55 men and 21 women and the mean age was 57.3 years (range, 32–82). All had a microscopic diagnosis of carcinoma of the lung.

[1]Received Sept 19, 1977; revised Jan 10, 1978; accepted Jan 30, 1978.

[2]Supported by Public Health Service grants CA-10044, CA-15691, and CA-16056 from the National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare.

[3]Departments of Medicine A (*Drs. Bjornsson, Preisler, Higby,* and *Henderson*) and Thoracic Surgery (*Drs. Takita* and *Catane*), Roswell Park Memorial Institute, Buffalo, NY.

[4]Millard Fillmore Hospital, Buffalo, NY.

[5]We wish to thank Dr. Peter Reese for his statistical assistance and Kathryn Czapski and Sandie Balera for their secretarial help.

**Reprint requests to:* Sigurdur Bjornsson, MD, Department of Medicine A, Roswell Park Memorial Institute, 666 Elm St, Buffalo, NY 14263.

TABLE 1.—Drug doses

Drug*	Dose
ADM	50 mg/m² iv
CTX	500 mg/m² iv
DDP	50 mg/m² iv with 1500–2000 ml of 5% dextrose in water + ⅓ normal saline, 37.5 g of mannitol, and 40 mg of Lasix
VCR	2 mg iv

*All drugs were given on the same day q4wks.

Patients were randomly assigned to one of three groups by a pre-arranged randomization technique. All patients were given the same CT, with ADM, CTX, DDP, and vincristine (VCR) administered every 4 weeks as described in table 1. Group A patients were given CT only, group B patients also received the methanol extracted residue (MER) of bacillus Calmette-Guérin (BCG) at a dose of 1 mg intradermally divided between five sites, and group C patients received *Corynebacterium parvum* (*C. parvum*) iv starting at a dose of 0.25 mg and escalated to 3 mg on subsequent visits. Pretreatment characteristics in the three treatment groups are summarized in table 2. Treatment was continued as long as a response or stable disease was maintained; ADM was discontinued when a dose of 550 mg/m² had been given (450 mg/m² in patients with prior radiation therapy to the chest). ADM and CTX doses were adjusted according to blood counts, DDP doses were modified according to creatinine clearance and audiograms, and ADM and VCR doses were decreased in the presence of decreased liver function.

A PR was defined as a ≥ 50% reduction in the product of perpendicular diameters of measurable lesions lasting 2 months without disease progression elsewhere. No change (NC) was defined as a < 50% reduction or no increase in the size of measurable lesions without progression anywhere for 2 months. Progressive disease (PD) was defined as progression

TABLE 2.—Patient characteristics

	Group			
	A	B	C	Totals
Total No. of patients	23	25	28	76
Sex				
Men	16	15	24	55
Women	7	10	4	21
Age	NS*			
Mean	61.2	55.1	60	57.3
Range	44–74	32–82	39–73	32–82
	NS*			
Mean performance†	2.11	1.96	1.70	1.90
Histology				
Adenocarcinoma	12	13	14	39
Squamous cell carcinoma	6	8	10	24
Large cell anaplastic carcinoma	4	3	3	10
Small cell anaplastic carcinoma	1	0	1	2
Unknown‡		1		1
Extent of disease				
Axillary/clavicular nodes	6 (26%)	8 (32%)	7 (25%)	21
Liver	3 (13%)	5 (20%)	4 (14%)	12
Brain	2 (9%)	1 (4%)	1 (4%)	4
Bone	10 (43%)	10 (40%)	11 (39%)	31
Prior therapy				
Resection	5	0	5	
Radiation and/or CT	12 (52%)	13 (52%)	11 (39%)	
		NS*		

*NS = not significantly different when analyzed by 1-way analysis of variance.

†Performance scale: 0 = no symptoms; 1 = symptoms, fully active; 2 = < 50% of daytime hrs in bed; 3 = ≥ 50% of daytime hrs in bed; 4 = bedridden.

‡Patient presented with superior vena cava syndrome; bronchoscopy was done; cytology was positive.

TABLE 3.—Response rate by histology

	Group											
	A (17 patients)				B (20 patients)				C (27 patients)			
	PR	NC	PD	ED†	PR	NC	PD	ED†	PR	NC	PD	ED†
Adenocarcinoma	1	3	5	3	3	1	6	3	2	9	3	
Squamous cell carcinoma	2	2	1	1	2	2	2	2		6	3	1
Large cell anaplastic carcinoma	1	1		2		2	1			2	1	
Small cell anaplastic carcinoma*	1								1			
Unknown					1							
Totals (%)	5(22)	6(26)	6(26)	6(26)	6(24)	5(20)	9(36)	5(20)	3(11)	17(61)	7(25)	1(4)

*Both patients previously treated.
†ED = early death, treatment failure.

in any site. All patients entered in the study were considered evaluable and were included in the survival graphs. The shortest followup was 8 months.

Since most of the patients lived outside of Buffalo, they had weekly blood counts done in their hometowns and returned to us only once monthly for treatment. Objective tumor response could, therefore, only be determined in those who came back at least once and thus had two or more treatment cycles.

The statistical significance of apparent differences in survival curves was tested by the Breslow life-table test (15).

RESULTS

Sixty-four patients (84%) had two or more courses of treatment. Of the other 12 patients (six in group A, five in group B, and one in group C), three died within 1 week of the first course, another six died within 1 month, and the remaining three died by 2 months. Table 3 shows the objective response rates among the three treatment groups, stratified by histologic type. No complete responses (CR) were seen. There were 14 PRs (18%), 28 NCs (37%), and 22 PDs (29%). Although PR was less commonly seen in group C, more patients in this group had NC and the PR + NC rate was 72% in group C versus 48% in group A and 44% in group B. Of note is that 11 of 14 (79%) of the adenocarcinoma patients treated with CT + *C. parvum* had PR or NC, whereas only four of 12 (33%) of the CT-alone patients and four of 13 (31%) of the CT + MER patients with the same histology achieved a comparable response. The median survival time (MST) was 53 weeks for PR patients, 34 weeks for NC patients, and 19 weeks for PD patients. The survival curves are different at the 0.001 level when tested by the Breslow test (fig 1).

The overall survival for the three treatment groups is shown in figure 2. The MST is 20 weeks in the CT-only group, 19 weeks in the CT + MER group, and 28 weeks in the CT + *C. parvum* group, the survival curves being significantly different at the 0.05 level (groups A or B versus C).

TOXICITY

CT-related toxicity was similar in all three groups. Virtually all patients had marked nausea, and vomiting was sometimes prolonged. No difference in wbc or platelet nadirs was observed among patients receiving MER or *C. parvum* compared to the CT-only group, and the actual amount of CT given was not different between the groups. Two patients had severe hematopoietic toxicity (wbc count $< 1000/\mu l$ and platelet count $< 75{,}000/\mu l$); both had previously received therapeutic doses of radiation therapy. Using the forced diuresis technique, no renal problems were encountered with DDP. The MER caused skin ulcerations and in a few patients minor temperature rise. *C. parvum* caused chills and fever in almost every patient. These side effects began 2–3 hours after the infusion but most patients were afebrile within 24 hours.

Two patients (one in group B and one in group C) died within 1 day of treatment; both were cardiac patients who were receiving their first course. One had arteriosclerotic heart disease, had suffered a myocardial infarct 7 years ago, and was receiving treatment for atrial fibrillation and congestive heart failure. Following the *C. parvum* infusion, his temperature and pulse rate rose to 38°C and 140/minute respectively, and he died in 2 hours. At autopsy he was found to have a large pulmonary embolus. The other patient also had congestive heart failure and a complete left bundle branch block. He developed a respiratory distress 8 hours

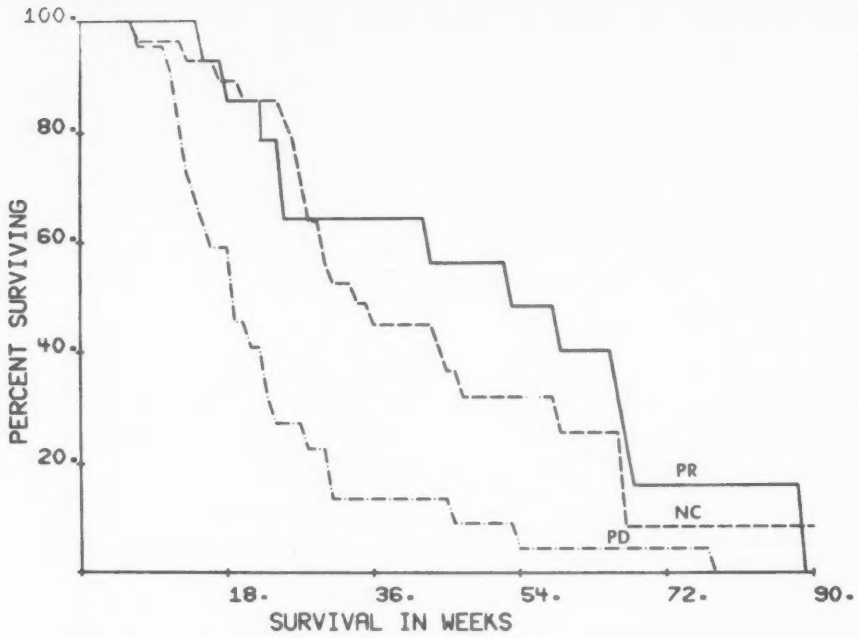


FIGURE 1.—Actuarial survival for 64 patients evaluable for response (≥ 2 treatment courses).

after receiving CT + MER and died. Permission for autopsy could not be obtained.

DISCUSSION

This combination CT-immunotherapy program required only one clinic visit per month and one visit for blood counts in the interval between treatments. In this study, only 18% of the patients showed a PR to treatment and none had a CR. There was, however, a large percentage of patients with a lesser response or stable disease who survived significantly longer than patients with PD. How much the treatment contributed to their more stable course is unknown but since recognizable pretreatment characteristics were not different in the three groups and assignment was by randomization, it must be assumed that any differences observed are treatment related.

While DDP is highly effective against various tumors (16), it has shown poor activity against non-small cell bronchogenic carcinoma when used alone (17) and mixed responses when used in combination with other agents (8,10). Nephrotoxicity of DDP, which was dose-limiting in earlier studies, can be avoided by the forced diuresis technique (18,19).

The main objective of this study was to determine the effects of MER and *C. parvum* on response rate and survival in lung cancer patients when given with CT. While MER had no effect on either parameter, the *C. parvum*-treated patients as a whole survived significantly longer even though their objective response rate was not improved. Although the overall survival time was increased by the administration of *C. parvum*, the percentage of long-term survivors is not different between the three treatment groups. These observations do support previous reports of favorable effects of *C. parvum* (8–11) and the lack of effect of BCG in inoperable lung cancer (20,21). We are currently studying whether the administration of *C. parvum* in-between rather than simultaneously with the CT courses may increase the benefit seen here.

C. parvum-induced chills and fever can be largely prevented by pretreatment with hydrocortisone (22), thereby increasing patient acceptability. Data from animal experiments suggest that the antitumor activity of *C. parvum* is unaffected by pretreatment with hydrocortisone (23).

In conclusion, the CT used in our study produced results similar to those reported by other investigators in terms of response rates and survival prolongation in responding patients. Survival among non-responders was similar to that of patients receiving

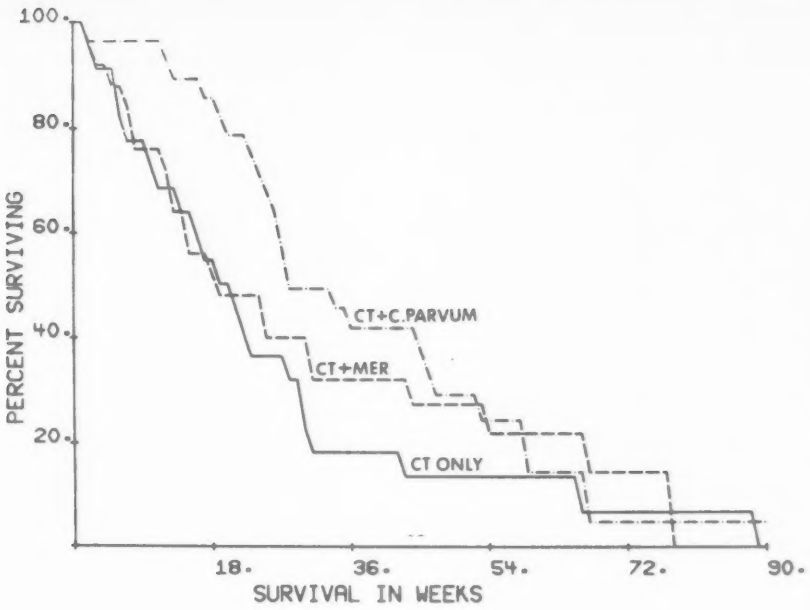


FIGURE 2.—Actuarial survival for all 76 study patients from start of therapy.

supportive treatment only (23). Patients treated with *C. parvum* had a longer overall survival than those treated with combination CT with or without MER. While the difference is statistically significant, the clinical impact is less impressive since long-term survival was not improved. We feel that *C. parvum* may be a useful agent in the management of advanced non-small cell carcinoma of the lung.

REFERENCES

1. LAING AH, BERRY RJ, NEWMAN CR, ET AL. Treatment of inoperable carcinoma of bronchus. Lancet 2:1161–1164, 1975.
2. SELAWRY OS. The role of chemotherapy in the treatment of lung cancer. Semin Oncol 1:259–272, 1974.
3. LIVINGSTON RB, FEE WH, EINHORN LH, ET AL. BACON (bleomycin, adriamycin, CCNU, Oncovin, and nitrogen mustard) in squamous lung cancer. Experience in fifty patients. Cancer 37:1237–1242, 1976.
4. BITRAN JD, DESSER RK, DEMEESTER TR, ET AL. Cyclophosphamide, adriamycin, methotrexate, and procarbazine (CAMP)—effective four-drug combination chemotherapy for metastatic non-oat cell bronchogenic carcinoma. Cancer Treat Rep 60:1225–1230, 1976.
5. MCMAHON LJ, JONES SE, DURIE B, ET AL. Combination chemotherapy with methyl-CCNU (NSC-94551), cyclophosphamide (NSC-26271), vincristine (NSC-67574), methotrexate (NSC-740), and bleomycin (NSC-125066) in advanced bronchogenic carcinoma. Cancer Lett 1:97–102, 1975.
6. LANZOTTI VJ, THOMAS DR, HOLOYE PY, ET AL. Bleomycin (NSC-125066) followed by cyclophosphamide (NSC-26271), vincristine (NSC-67574), methotrexate (NSC-740), and 5-fluorouracil (NSC-19893) for non-oat cell bronchogenic carcinoma. Cancer Treat Rep 60:61–68, 1976.
7. CHAHINIAN AP, ARNOLD DJ, COHEN JM, ET AL. Chemotherapy for bronchogenic carcinoma: methotrexate, doxorubicin, cyclophosphamide, and Lomustine. JAMA 237:2392–2396, 1977.
8. WALLACE HJ, JR, HIGBY DJ, WILBUR DW, ET AL. Adriamycin (ADM)-*cis*-dichlorodiammineplatinum II (DDP) and adriamycin-cyclophosphamide (CYT) combinations in the chemotherapy of advanced cancer. Proc Am Assoc Cancer Res and ASCO 16:244, 1975.
9. GREEN RA, HUMPHREY E, CLOSE H, ET AL. Alkylating agents in bronchogenic carcinoma. Am J Med 46:516–525, 1969.
10. PIEL IJ, and PERLIA CP. Phase II study of *cis*-dichlorodiammineplatinum(II) (NSC-119875) in combination with cyclophosphamide (NSC-26271) in the treatment of human malignancies. Cancer Chemother Rep 59:995–999, 1975.
11. HERSH EM, GUTTERMAN JV, and MAVLIGIT GM. Perspectives in immunotherapy of lung cancer. Cancer Treat Rev 1:65–80, 1974.
12. ISRAËL L, EDELSTEIN R, DEPIERRE A, ET AL. Brief Communication: Daily intravenous infusions of *Corynebacterium parvum* in twenty patients with disseminated cancer: a preliminary report of clinical and biologic findings. J Natl Cancer Inst 55:29–33, 1975.
13. DIMITROV NV, CONROY J, SUHRLAND LG, ET AL. Combination therapy with *Corynebacterium parvum* and doxorubicin hydrochloride in patients with lung cancer. *In* Immunotherapy of Cancer: Present Status of Trials in Man (Terry WD, and Windhorst D, eds). New York, Raven Press, 1978, pp 181–190.

14. TAKITA H, and MOAYERI H. Effects of *Corynebacterium parvum* and chemotherapy in lung carcinoma. Proc Am Assoc Cancer Res and ASCO 17:292, 1976.
15. BRESLOW N. A generalized Kurskal-Wallis test for comparing K samples subject to unequal patterns of censorship. Biometrika 57:579, 1970.
16. ROZENCWEIG M, VON HOFF DD, SLAVIK M, ET AL. *Cis*-diamminedichloroplatinum (II). A new anticancer drug. Ann Intern Med 86:803–812, 1977.
17. ROSSOF AH, BEARDEN JD III, and COLTMAN CA, JR. Phase II evaluation of *cis*-diamminedichloroplatinum(II) in lung cancer. Cancer Treat Rep 60:1679–1680, 1976.
18. MERRIN C. A new method to prevent toxicity with high doses of *cis*-diammineplatinum (therapeutic efficacy in previously treated widespread and recurrent testicular tumors). Proc Am Assoc Cancer Res and ASCO 17:243, 1976.
19. HAYES D, CVITKOVIC E, GOLBEY R, ET AL. Amelioration of renal toxicity of high dose *cis*-platinum diammine dichloride (CPDD) by mannitol induced diuresis. Proc Am Assoc Cancer Res and ASCO 17:169, 1976.
20. PINES A. A 5-year controlled study of B.C.G. and radiotherapy for inoperable lung cancer. Lancet 1(7956):380–381, 1976.
21. MCKNEALLY MF, MAVER C, and KAUSEL HW. Regional immunotherapy of lung cancer with intrapleural B.C.G. Lancet 1(7956):377–379, 1976.
22. FISHER B, RUBIN H, SARTIANO G, ET AL. Observations following *Corynebacterium parvum* administration to patients with advanced malignancy. Cancer 38:119–130, 1976.
23. FISHER B, RUBIN H, SAFFER E, ET AL. Further observations on the inhibition of tumor growth by *Corynebacterium parvum* with cyclophosphamide. II. Effect of cortisone acetate. J Natl Cancer Inst 56:571–574, 1976.

Intracellular Localization of *meso*-Tetra(*p*-sulfophenyl)porphine: A Potential Tumor Localizing Agent [1,2]

Jack D. Austen,[3] Stewart McConnell,[3] Carl J. Carrano,[3,4] and Minoru Tsutsui [3,5,*]

SUMMARY

The mechanism of *meso*-tetra (*p*-sulfophenyl)porphine ($TPPS_4$) localization was examined in Vero and HEp-2 cells in vitro. $TPPS_4$ was found to be relatively nontoxic to both cell types at concentrations up to 200 μg/ml. However, changes in cellular ultrastructure were observed by electron microscopy, consisting mainly of an increase in membrane-bound vacuoles. The nature of the new structures has not been determined. Both fluorescence microscopy and cellular fractionation indicate that $TPPS_4$ is localized inside the cells studied. Considerable differences in the pattern of localization between the two cell types were found. The $TPPS_4$ in the Vero cells was found to be mainly in the soluble fraction and the red fluorescence was found to be diffuse throughout the cytoplasm. The HEp-2 cells showed $TPPS_4$ fluorescence associated with various cell organelles, predominantly the nucleolus. [^{14}C]-$TPPS_4$ was found in many cellular components but predominantly it was in the soluble and protein fractions. These differences may be significant in the understanding of in vivo localization of this porphyrin in neoplastic tissue.

[Cancer Treat Rep 62:511–518, 1978]

The selective localization of well-defined chemical materials in malignant tumors has been a long-range objective of many lines of research. It has been found that many naturally occurring porphyrins appear to possess an affinity for neoplastic tissue (1). Winkelman et al have shown that the synthetic porphyrin TPPS[6] is found to localize in the tumors of rats bearing the Walker 256 carcinoma (2,3). Tumor to tissue ratios of $\geq 4:1$ are reported. TPPS has many advantages over hematoporphyrin, the most commonly used natural porphyrin. These include increased water solubility at neutral pH, ease of synthesis, and increased absolute concentration in tumors. The potential uses of such a compound in a diagnostic or chemotherapeutic role are great (4–6). Unfortunately, although the phenomenon of porphyrin localization in tumors has been observed for over half a century, little is known about it on a cellular level. The use of cells grown in tissue culture provides a means for examination of the effects of *meso*-tetra(*p*-sulfophenyl)porphine ($TPPS_4$) on cells without the complications inherent in an in vivo study. This work was undertaken to determine the intracellular localization of this porphyrin in several cell types in hopes of elucidating the mechanism of its localization into tumor tissue.

EXPERIMENTAL PROCEDURES

Both the Vero (African green monkey kidney) and the HEp-2 (human larynx, epidermoid carcinoma) cells were obtained from the American Type Culture Collection (Rockville, Md) as certified cell lines

[1]Received Aug 3, 1977; revised Jan 10, 1978; accepted Jan 24, 1978.

[2]Supported by National Institutes of Health Biomedical grant 55142 and Robert A. Welch Foundation grant A-420.

[3]Departments of Veterinary Microbiology (*J. D. Austen* and *S. McConnell*) and Chemistry (*C. J. Carrano* and *M. Tsutsui*), Texas A and M University, College Station.

[4]University Health Fellow, Texas A and M University. This work is in partial fulfillment of the requirements for a doctoral degree.

[5]We would like to acknowledge the excellent assistance of Mrs. Georgia Cummings and Mrs. Kim Bennett.

[6]TPPS refers to an unpurified mixture of tetraphenylporphine sulfonates.

**Reprint requests to:* Dr. Minoru Tsutsui, Department of Chemistry, Texas A and M University, College Station, Tex 77843.

CCL81 and CCL23, respectively. The Vero cell was chosen for its density-dependent inhibition of growth. It is well studied, completely characterized, and used extensively in viral replication studies. The HEp-2 cells, which do not display density-dependent inhibition of growth and were derived from human neoplastic tissue (7), were used for comparative purposes. The cells were cultured in minimum essential medium supplemented with 2% fetal bovine serum, 3% calf serum, 1% Kantrex, and 0.25% Hepes[7] (Vero cells) or Eagle's basal medium with 5% fetal bovine serum, 5% calf serum, 1% penicillin, and 1% streptomycin (HEp-2 cells). Cells were subcultured on the third day into Leighton tubes, soft glass bottles, or scintillation vials, depending on the experiment, at a density of 2×10^5 cells/ml. Confluent monolayers were re-fed and tested in a standardized L-15 (Liebovitz) medium, supplemented with 2% agamma newborn bovine serum, 1% L-glutamine, 1% penicillin, and 1% streptomycin. Cells were incubated at 37°C in the dark due to the known photosensitivity of cells containing high levels of porphyrins. Cell numbers were counted by removing cells from vials using a 0.05% trypsin solution in phosphate buffered saline (PBS)[8] with 0.5 mM EDTA, removing an aliquot, and counting in a hemocytometer or electronic Coulter Counter. Cell viability was determined by the Trypan blue dye exclusion technique and viral challenge studies.

Intracellular Localization

Cells were grown as previously described in 16-oz bottles and were exposed to [^{14}C]-$TPPS_4$ (100 μg/ml; specific activity, 0.01 microcurie/ml) for time periods ranging from 8 to 48 hours. The cells were harvested and fractioned chemically by a modification of the method of Renshaw and Thompson (8). This produced a cold trichloroacetic acid (TCA)-soluble fraction (small molecules), a hot TCA-soluble fraction (nucleic acids), an ethanol/ether fraction (lipids), and a TCA-insoluble fraction (proteins). Results were calculated as percentage of total radioactivity recovered incorporated into each fraction. Radioactivity was measured by liquid scintillation counting. Dried samples of each fraction were placed in a vial and 10 ml of a scintillation cocktail consisting of 2 g/liter of PPO and 50 mg/liter of POPOP in scintillation grade toluene were added. The samples were then counted on a Beckman LS-100 liquid scintillation counter using the ^{3}H/^{14}C window. Quenching was calibrated by the external standard ratio method.

Fluorescence Microscopy

Cells were grown on coverslips in Leighton tubes as previously described. They were then exposed to $TPPS_4$ (50 μg/ml) for various lengths of time. The slips were removed, washed three times with PBS (pH 7.2), and wet mounted on slides for observation under an oil immersion ultraviolet (UV) microscope (Leitz, BG-12 and OG-9 filters) for the characteristic red fluorescence. Photographs were taken using 540 × magnification with Kodak high-speed Ektachrome (ASA 160) and a 2-minute exposure.

Electron Microscopy

Cells were prepared for electron microscopy as described by Hayat (9).

Binding to Nucleic Acids

Various concentrations of $TPPS_4$ were added to 1-mg/ml solutions of RNA (Sigma, yeast Type XI) and DNA (Sigma, calf thymus type V) in 0.025 M phosphate and 0.2 M NaCl buffer. $TPPS_4$ was monitored for any perturbation in the Soret band of its visible spectra, either as band broadening or as wavelength shift. Nucleic acids were monitored by examination of their UV spectra. Equilibrium dialysis experiments were performed as follows: 5-ml portions of nucleic acids at a concentration of 1 mg/ml in buffer were placed in dialysis bags (Fisher No. 8-667C); 25 ml of a $TPPS_4$ solution in the same buffer was added to a flask at concentrations of 20, 40, 80, 200, and 400 μg/ml. The dialysis bag was then placed in the flask and allowed to reach equilibrium. After 10 days, the concentrations of $TPPS_4$ both inside and outside the bag were monitored by measuring absorbance at 414 nm.

Synthesis

Tetraphenylporphine (TPP) was prepared by the method of Adler et al (10). ^{14}C-labeled TPP was prepared by the following modification. One millicurie of [^{14}C]-benzaldehyde (28.8 mg) as the sodium bisulfite addition compound was hydrolyzed by the addition of 0.5 ml of 10% sodium carbonate, with warming. The solution was then neutralized with propionic acid. The labeled solution was added to refluxing propionic acid with 1.6 ml (0.013 mol) of unlabeled benzaldehyde as a carrier and 1.1 ml of redistilled pyrrole. Reflux was continued for 30

[7] Hepes = *N*-2-hydroxyethyl piperazine-*N*-2-ethanesulfonic acid.

[8] Consisting of NaCl, 8.0; KCl, 0.3; Na_2HPO_4, 0.073; KH_2PO_4, 0.02; and glucose, 2.0 (all units are g/liter).

minutes; the mixture was cooled overnight and filtered. The violet crystals were washed with hot methanol and water and air dried: yield, 0.467 g (22%).

$TPPS_4$ was prepared by the method of Srivastava and Tsutsui (11). Briefly, this consisted of heating TPP in excess concentrated sulfuric acid at 90°C for 8–10 hours and allowing it to stand for 12 hours. This was followed by neutralization with calcium oxide. This procedure leaves a very crude product contaminated with inorganic salts. The $TPPS_4$ prepared was purified by chromatography on Sephadex LH-20. The impurities separate out a yellow fraction prior to a red fraction containing the product. Only a single spot corresponding to the pure tetrasulfonated isomer is found on thin layer chromatography using the system described by Winkelman et al (3). ^{14}C-labeled $TPPS_4$ was prepared by the same procedure using the entire 0.467 g of labeled TPP from the previous step. This yielded 0.272 g (specific activity, 0.1 microcurie/mg).

All visible spectra were run on a Beckman Model 24 spectrophotometer using 1-cm cells. PPO was purchased from J. T. Baker Chemical Co, and POPOP from Aldrich Chemical Co. The [^{14}C]-benzaldehyde was a product of ICN Pharmaceuticals, Inc.

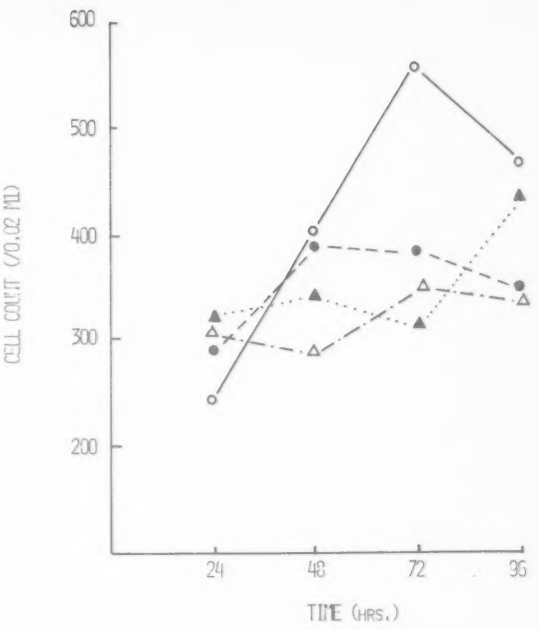


FIGURE 1.—Cell counts of $TPPS_4$-treated and untreated Vero and HEp-2 cells: ○ = untreated Vero; ● = treated Vero; △ = untreated HEp-2; and ▲ = treated HEp-2.

RESULTS

Acute Toxicity In Vitro

Several studies were performed to determine any possible acute toxicity of $TPPS_4$ on the cell lines tested. All toxicity studies were made in duplicate, and parallel untreated control cells were examined simultaneously for comparative purposes. Concentrations of $TPPS_4$ ranging from 10 to 200 μg/ml were added to the growth media (L-15) of cells grown on glass coverslips. Both treated and untreated HEp-2 and Vero cells were examined daily for obvious cytopathic effects. No such effects were observed for either cell type at any concentration.

Viability of treated cells was confirmed by the Trypan blue dye exclusion technique. Trypan blue staining showed approximately 90% viable cells for both cell lines at all concentrations of $TPPS_4$ tested.

The viability of the treated cells was also ascertained by the ability of the cell sheet to replicate viruses to which the cells are susceptible. Virus susceptibility studies were conducted in both treated and untreated cell populations after 4-day exposure to $TPPS_4$ (50 μg/ml). The virus inoculum used was the vaccine strain (TC83) of Venezuelan equine encephalitis virus. Cell monolayers were examined daily for evidence of virus-induced cytopathic effects. A similar cytopathogenic effect was evident in both treated and untreated cell populations.

The Vero cells treated with $TPPS_4$ and subcultured 4 days later showed a significant reduction in viable cell counts when compared to untreated parallel controls. Subsequent subculturing without further treatment resulted in a regrowth to normal cell counts. Figure 1 shows cell numbers of a trypsinized cell suspension versus time for both treated and untreated cells. The untreated Vero cells are in a rapidly dividing state with a doubling time of about 24 hours. After 72 hours, the cell sheet has reached confluency and the number of cells is reduced at longer times. The $TPPS_4$-treated Vero cells show a significant reduction in cell number after about 48 hours of exposure. The untreated HEp-2 cells, however, show a nearly constant cell population as measured by Coulter Counter counts. The HEp-2 cells represent a rapidly dividing cell sheet but are known to form a multilayer and to be only loosely attached to the substrate. Thus, when washing to remove media, etc, prior to trypsinizing, many cells are lost, resulting in an apparently constant population. The treated HEp-2 cells show an increase in cell number with increasing time of

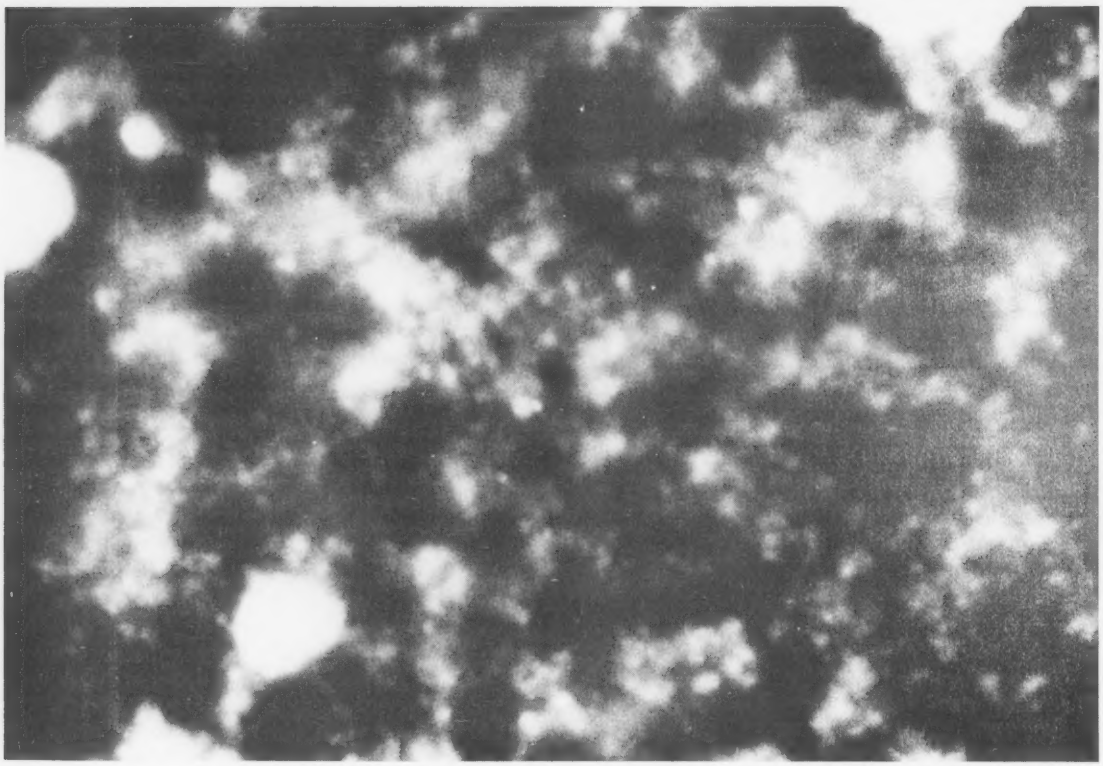


FIGURE 2.—Black and white reproduction of the fluorescence photomicrograph of Vero cells; oil immersion, 2-min exposure. White areas = red fluorescing areas in original color photograph (× 540).

exposure of $TPPS_4$. This is consistent with the increasing strength of attachment between cells and glass on treatment with $TPPS_4$ (Tsutsui, et al, unpublished observation).

Light and Fluorescence Microscopy

Vero and HEp-2 cells treated with $TPPS_4$ (50 μg/ml for 48 hours) and then stained with May-Grünwald-Giemsa showed no apparent abnormalities when compared with untreated controls. Normal cell structure was observed in both treated and untreated cells, with the nucleolus and nucleus clearly defined.

The untreated HEp-2 cells showed a faint green auto-fluorescence while no visible emission was observed for the untreated Vero cells when examined under UV light. A characteristic red fluorescence could be observed in both cell types upon treatment with $TPPS_4$. This fluorescence was dose-dependent, with the emission intensity increasing with the increasing $TPPS_4$ concentration (10–200 μg/ml). A concentration of 50 μg/ml was found to be most satisfactory for visible and photographic observation and was used in all subsequent experiments. The fluorescence was also found to be pH dependent, with a pH optimum of 7.0–7.2. At higher or lower pH levels, the intensity level fell rapidly.

Vero cells showed a mottled pattern of fluorescence with evidence of vacuolization in the cytoplasm (fig 2). The fluorescence was granular in appearance and no distinct cell structure or outline could be observed. In contrast, the HEp-2 cells showed a distinct staining by $TPPS_4$ (fig 3). Most cell structures were clearly defined. Maximum red fluorescence occurred in the nucleolus with progressively less in the nucleus and cytoplasm. Cells that were treated for 48 hours and then placed in fresh media and observed at various times showed a slow reduction in apparent fluorescence intensity for the first several hours, and a more rapid loss over the next 48 hours. Cells treated with $TPPS_4$ for 48 hours

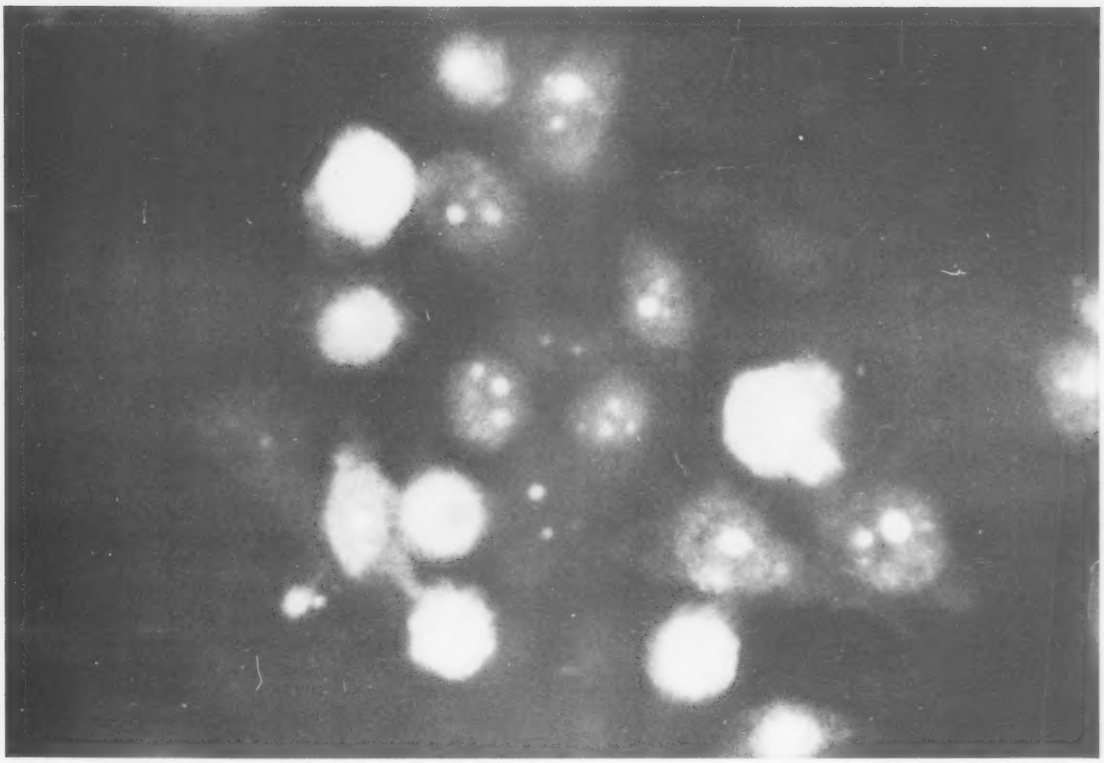


FIGURE 3.—Black and white reproduction of the fluorescence photomicrograph of HEp-2 cells; oil immersion, 2-min exposure. White areas = red fluorescing areas in original color photograph (× 540).

and then subcultured and regrown in fresh media without $TPPS_4$ showed only an occasional faintly red cell in the daughter generation.

Electron Microscopy

Cytologic changes in treated Vero and HEp-2 cells were observed by electron microscopy. Normal cellular morphology and architecture are found in untreated cell monolayers (fig 4A). The cells exposed to $TPPS_4$ (50 μg/ml) appear to have an altered profile (fig 4, B, C, and D) with the major effects being on the mitochondria and endoplasmic reticulum. The treated cells are characterized by a reduced number of mitochondria and an increased incidence of membrane-bound vacuoles. The origin and significance of these structures which contain many darkly stained invaginations are still obscure. These new structures may be damaged or degenerated mitochondria, based on the size and apparent reduction in the numbers of such organelles in the treated cells.

$TPPS_4$-treated cells are further characterized by a swollen disfigured endoplasmic reticulum. What effect this has on the cell is unknown.

Intracellular Localization

Electron and fluorescence microscopy gave indications that the porphyrin was localized intracellularly, specifically in the cytoplasm and in the nucleolus. However, the phenomena of increased attachment of treated cells to glass and their resistance to lysis suggested membrane-bound $TPPS_4$. Intracellular localization was determined by a chemical extraction procedure. After 48 hours of exposure to [^{14}C]-$TPPS_4$, the Vero and HEp-2 cells showed different patterns of localization within the cell components (table 1).

Most of the label in the Vero cells was found in the cytosol with only a small amount in the lipid or protein fractions, and a moderate amount associated with the nucleic acids. This indicates very little attachment, at this point, to any cellular structure,

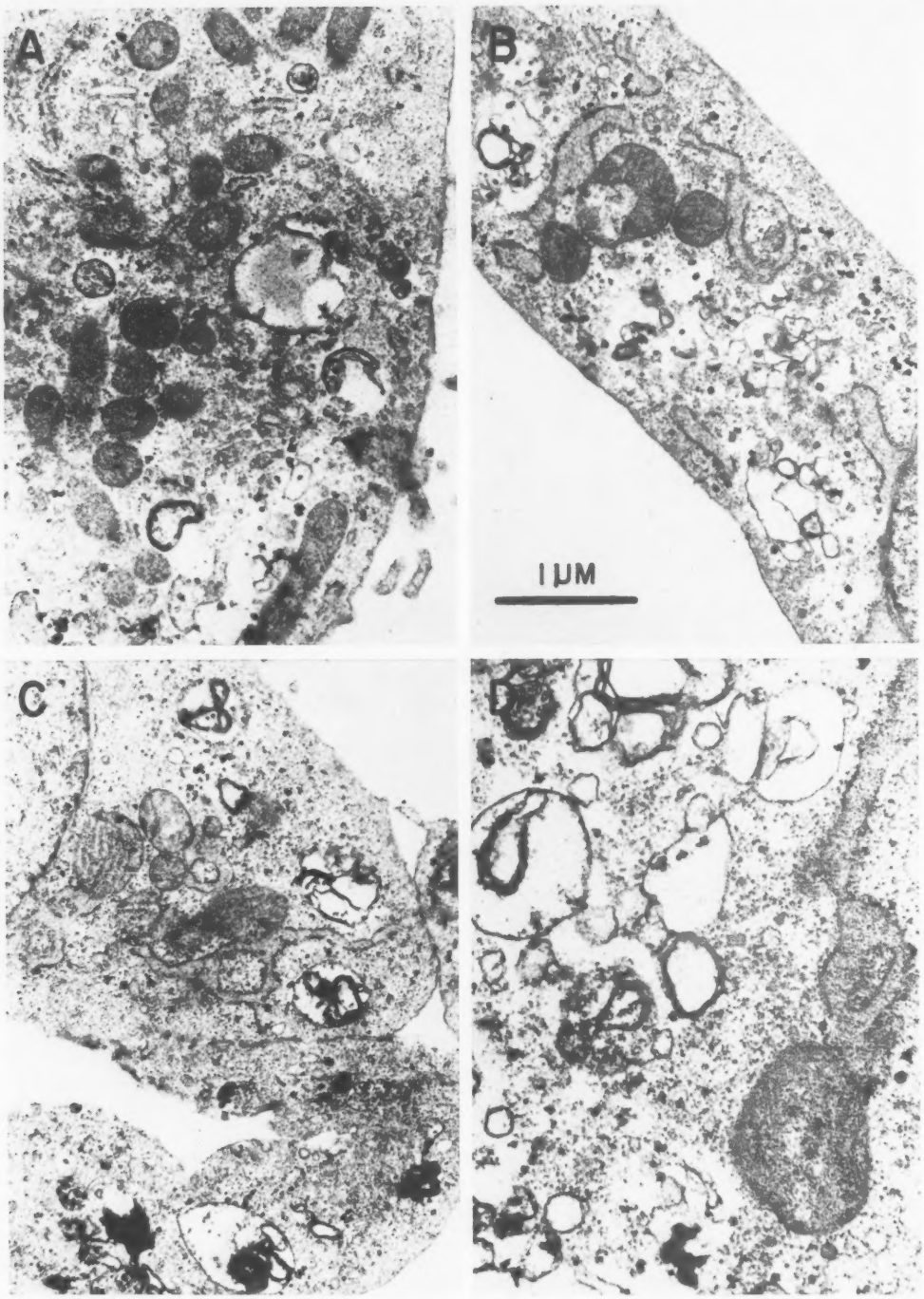


FIGURE 4.—A. Electron micrograph of untreated Vero cells (× 10,000). B. Electron micrograph of Vero cells treated with 50 μg/ml of $TPPS_4$. Note membrane-bound vacuoles and endoplasmic reticulum (× 10,000). C. Electron micrograph of HEp-2 cells treated with 50 μg/ml of $TPPS_4$. Note the incidence of membrane-bound vacuoles (× 10,000). D. Electron micrograph of Vero cells treated with 50 μg/ml of $TPPS_4$ showing detailed structure of membrane-bound vacuoles (× 18,000).

TABLE 1.—Intracellular localization of $TPPS_4$ (100 μg/ml) after 48 hrs

Component*	% radioactivity	
	Vero cells†	HEp-2 cells
Cold TCA soluble (metabolic intermediates)	67	54
Hot TCA soluble (nucleic acids)	22	4
Ethanol/ether soluble (lipids)	4	4
Residue (protein)	5	38

*As described in the text.
†Average of 2 determinations.

in agreement with the fluorescence microscopy observations. The HEp-2 cells show a markedly different pattern, with about half of the label in the cytosol or only weakly bound to any structure, and the bulk of the remainder associated with the protein. Again, this is in agreement with microscopic evaluation. The low levels of $TPPS_4$ in the lipid fraction at all times would seem to indicate little or no membrane-bound $TPPS_4$, but this may be an artifact of the procedure. $TPPS_4$ bound to membranes would be expected to exist as a lipoprotein complex, and selective extraction of the lipid portion may disrupt the complex and its geometry, leaving $TPPS_4$ seemingly unassociated with the membrane.

Interaction of $TPPS_4$ With Nucleic Acids

The fluorescence microscopy indicated that $TPPS_4$ might be highly concentrated in the nucleolus, based on visible fluorescence. Binding of $TPPS_4$ to nucleic acids was examined by UV-visible spectroscopy and equilibrium dialysis. No detectable differences in either the visible spectrum of $TPPS_4$ or the UV spectra of DNA or RNA were observed when various concentrations of porphyrin and nucleic acids were mixed. Equilibrium dialysis also revealed no detectable binding between DNA, RNA, and $TPPS_4$ at several concentrations. Thus, we conclude that $TPPS_4$ is not bound appreciably to nucleic acids under the conditions studied, in agreement with the intracellular localization studies.

DISCUSSION

In order to fully understand the mechanism of tumor-localizing agents, it becomes necessary to understand their behavior on a cellular level. The use of mammalian cells grown in tissue culture provided a direct means for studying the interactions of TPP sulfonate with homogeneous populations of cells, uncomplicated by all the variables inherent in an in vivo study. $TPPS_4$ was found to be generally nontoxic to cells exposed to concentrations ranging up to 200 μg/ml, although it was found to have an effect on the growth rate of Vero cells. The treated cells did not reach populations equivalent to those of the untreated controls, but were found to regrow to normal cell counts on removal of $TPPS_4$. This may reflect the cytologic changes in treated cells found by electron microscopy. The reduction in the apparent number of mitochondria and the swelling of the endoplasmic reticulum are the two most obvious effects. Since the mitochondria are the site of cellular respiration and energy production, and the endoplasmic reticulum is the site of protein synthesis (via ribosomes), it is not surprising that $TPPS_4$ would have an effect on the growth rate of cells exposed to it.

Another possibility is that of singlet oxygen-induced photo-oxidative damage caused by porphyrin photosensitization. Porphyrins are known photosensitizers and singlet oxygen has been demonstrated to be the active agent (12). Slater and Riley (13) have shown that the porphyrin, phylloerythrin, induces lysosomal rupture. Other intracellular structures most notably damaged by photo-oxidative reactions are the endoplasmic reticulum and the mitochondria.

Classically, a large hydrophilic molecule such as $TPPS_4$ would not be expected to penetrate the lipid-rich cell plasma membrane. However, several independent lines of evidence suggest that $TPPS_4$ is indeed transported into the cytoplasm of at least two cell types, and is not located primarily on cell membranes. First, the fluorescence microscopic evaluation of Vero and HEp-2 cells treated with $TPPS_4$ indicates intracellular porphyrin. This is most clearly evident in the HEp-2 cells, where fluorescence staining of the nucleolus, nucleus, and cytoplasm occurs. Contrary to what might be expected, the bright fluorescence observed by us in the nucleolus of cells does not appear to reflect any binding to nucleic acids. This has been adequately demonstrated by the intracellular localization, difference spectroscopy, and equilibrium dialysis experiments. However, the nucleolus is only 5%–10% RNA with the remainder being protein (14). This protein is presumably richly basic as it must bind the negatively charged RNA much as the histones do for DNA. The $TPPS_4$ could be expected to form a tight complex with such a protein, perhaps resulting in an increase in the fluorescence intensity due to an increased hydrophobic environment around the porphyrin. These organelles can be stained only due to $TPPS_4$ that enters the cell proper. Secondly, the $TPPS_4$-induced changes in cellular ultrastructure

discovered by electron microscopy also indicate intracellular material. Finally, the localization study indicates that porphyrin is bound to all fractions of cellular components to a degree. There are generally high levels in the protein and soluble fractions, with less associated with the nucleic acids and lipids. Winkelman reports that hematoporphyrin is located mainly in the soluble fraction of Walker 256 carcinoma cells 24 hours following injection (15). He found 63% in the soluble phase and about 15% associated with the nuclei. This compares closely with the 67% $TPPS_4$ found in the soluble fraction and 22% found associated with nucleic acids for the Vero cells after about 48 hours. In addition, he observed a diffuse red fluorescence under UV microscopic evaluation. This is in agreement with our results on Vero cells. This pattern of localization was found to change with time, indicating that $TPPS_4$ ingested is not static, but moves from one cellular compartment to another. Whether this reflects metabolism, perhaps by aryl sulfatases contained in lysosomes, excretion, or incorporation into cellular material is presently unknown. Winkelman has provided evidence that metabolism does not occur (16), but we have found that porphyrin fluorescence fades with time when ingested. This is in agreement with Albert who has demonstrated that $TPPS_4$ fluorescence in elastic tissue is stable if cellular metabolism is stopped (ie, cells that have been fixed and embedded in plastic) but not if cells are actively metabolizing (17).

Although $TPPS_4$ was not expected to be able to diffuse across the cell membrane, mechanisms do exist for the transport of such large, hydrophilic molecules. These possibilities were examined by a kinetic analysis of the uptake of $TPPS_4$ in two cell types. These results will be presented in a forthcoming paper.

REFERENCES

1. TSUTSUI M, CARRANO CJ, and TSUTSUI EA. Tumor localizer: porphyrins and related compounds (unusual metalloporphyrins XXIII). Ann NY Acad Sci 244:674–684, 1975.
2. WINKELMAN J. The distribution of tetraphenylporphinesulfonate in the tumor-bearing rat. Cancer Res 22:589–596, 1962.
3. WINKELMAN J, SLATER G, and GROSSMAN J. The concentration in tumor and other tissues of parenterally administered tritium and C-14 labeled tetraphenylporphinesulfonate. Cancer Res 27:2060–2066, 1967.
4. WEISHAUPT KR, GOMER CJ, and DOUGHERTY TJ. Identification of singlet oxygen as the cytotoxic agent in photoinactivation of a murine tumor. Cancer Res 36:2326–2329, 1976.
5. DOUGHERTY TJ, GOMER CJ, and WEISHAUPT KR. Energetics and efficiency of photoinactivation of murine tumor cells containing hematoporphyrin. Cancer Res 36:2330–2333, 1976.
6. KAUFMAN J, DOUGHERTY T, GOLDFARB A, ET AL. Photoradiation therapy of malignant tumors. Proc Am Assoc Cancer Res and ASCO 18:275, 1977.
7. SHANNON JE, ed. ATTC Registry of Animal Cell Lines, 2nd ed. CCL 23, 1972.
8. RENSHAW E, and THOMPSON AJ. Tracer studies to locate the site of platinum ions within filamentous and inhibited cells of *Escherichia coli*. J Bacteriol 94:1915–1918, 1967.
9. HAYAT MA. Principles and Techniques of Electron Microscopy: Biological Applications. New York, Van Nostrand Reinhold Co, vol 1, 1970.
10. ADLER AD, LONGO FR, and FINARELLI JD. A simplified synthesis of *meso*-tetraphenylporphine. J Org Chem 32:476, 1976.
11. SRIVASTAVA TJ, and TSUTSUI M. Preparation and purification of tetrasodium *meso*-tetra(*p*-sulfophenyl)porphine. An easy procedure. J Org Chem 38:2103, 1973.
12. SUWA K, KIMURA T, and SCHAAP AP. Reactivity of singlet molecular oxygen with cholesterol in a phospholipid membrane matrix. A model for oxidative damage of membranes. Biochem Biophys Res Commun 75:785–791, 1977.
13. SLATER TF, and RILEY PA. Photosensitization and lysosomal damage. Nature 209:151–154, 1966.
14. NOVIKOFF AB, and HOLTZMAN E. Nuclei and ribosomes. *In* Cells and Organelles. New York, Holt, Reinhart and Winston, 1970, p 70.
15. WINKELMAN J. Intracellular localization of "hematoporphyrin" in a transplanted tumor. J Natl Cancer Inst 27:1369–1377, 1961.
16. WINKELMAN J. Metabolic studies on the accumulation of tetraphenylporphinesulfonate in tumours. Experientia 23:949, 1967.
17. ALBERT EN. A combined fluorescent and electron microscopic stain for elastic tissue. Histochem J 5:157–167, 1973.

Studies of the Growth, Population Kinetics, and Host Lethality of $CD8F_1$ Mammary Adenocarcinoma[1,2]

L. Simpson-Herren,* D. P. Griswold, Jr, and T. H. Corbett[3,4]

SUMMARY

First-generation transplants of spontaneous mammary adenocarcinomas in $CD8F_1$ mice have been included in the tumor panel used for the screening of potential anticancer chemotherapeutic agents. Studies were undertaken to evaluate the growth and kinetic characteristics to provide a better understanding of the basic biology of the tumor system. The spontaneous mammary adenocarcinomas are highly variable in growth rate, and this characteristic is seen to a lesser extent in the transplanted tumors. The doubling time of the transplants is usually, but not always shorter than the doubling time of the donor tumor at a similar mass. The median length of the cell cycle obtained from pooled data from first-generation transplants of four donor tumors is 15.6 hours with a median S phase of 9.5 hours. The thymidine indices (TI) ranged from a mean of 0.28 at 100 mg to a mean of 0.20 when tumors ranged from 3 to 6 g. The mean TI of tumors of all sizes is 0.27. The cell cycle parameters and TIs appear to be characteristic of the tumor system and apparently do not vary with characteristics of the donor tumor. These studies also indicate that these kinetic parameters are not responsible for the variation in volume doubling time of the transplanted tumors.

[Cancer Treat Rep 62:519–528, 1978]

The search for animal tumors which might serve as biologic and therapeutically predictive models for the various cancers of man has been long, and the likely validity of these animal tumor models remains a controversial issue. One of the major controversies has to do with the use of spontaneous or induced tumors as opposed to transplantable tumors. Wexler et al (1,2) have studied the biologic behavior, particularly tumor growth rates, metastatic tendencies, and effects on host lifespan, of several spontaneous, chemically induced, and transplantable mouse tumors. Although the tumors in each of those three categories differed in a number of respects, major differences were in degree. Continued transplantation clearly selected more uniform and predictable tumor behavior. Their experience led them to suggest that in experiments involving "surgical methods," large numbers of animals and uniform tumor growth are requirements which generally limit the use of either induced or spontaneous tumors. A similar case could be made for chemotherapy trials or surgery/chemotherapy trials. Scholler et al (3), on the other hand, urged caution in the use of transplantable tumors for chemotherapy trials because of the qualitative and quantitative changes that tend to follow repeated tumor transplantation.

Regardless of biochemical, biologic, or morphologic similarities, the determination of the usefulness of an animal tumor as a predictive model for the selection of new chemotherapeutic agents can only be made in retrospect after comparison of the tumor responses of man and animal to chemotherapy. Correlation must be evident in both positive

[1] Received Aug 25, 1977; revised Jan 3, 1978; accepted Jan 11, 1978.

[2] Supported by contract N01-CM-43756 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare.

[3] Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Ala.

[4] We thank B. J. Roberts for the animal studies, T. Springer, J. P. Holmquist, and A. H. Sanford for the thymidine studies, and L. Muglach for typing the manuscript.

*_Reprint requests to:_ Mrs. Linda Simpson-Herren, Cell and Tissue Kinetics Section, Southern Research Institute, 2000 9th Ave S, Birmingham, Ala 35205.

and negative responses. Schabel (4) has recently noted that "... direct positive correlation between any experimental tumor system and any specific histologic type of human cancer has not been clearly shown. This fact notwithstanding, general principles appear to be broadly valid in biology, and ... reproducible observations in animals (may be considered) as likely indications of principles applicable to human disease, and therapeutic responses in animals as probably useful indicators of response in man."

In spite of the difficulties involved, the search for new, potentially useful animal tumor models continues. One model that has gained recent consideration is the spontaneous mammary adenocarcinoma of $CD8F_1$ mice (BALB/cf C3H × DBA/8). This animal tumor system, developed by Martin and his colleagues (5,6) at the Catholic Medical Center, has previously been described in detail.

It was our purpose, in the studies reported here, to study the biologic characteristics of this tumor. Particular emphasis was placed on growth rates and kinetics of the first-generation transplants, especially those characteristics that might influence the interpretation of chemotherapeutic results.

MATERIALS AND METHODS

Biologic Systems

Mammary adenocarcinomas arise spontaneously in female $CD8F_1$ (BALB/cf C3H × DBA/8) mice. The BALB/cf C3H strain was originally infected with mammary tumor virus by foster nursing on virus-infected C3H mothers; this strain shows a high incidence of mammary tumors. The DBA/8 strain was infected by neonatal ingestion of mammary tumor virus-infected tissue extracts. Females of this strain have a low incidence of mammary tumors. The BALB/cf C3H and the DBA/8 strains have been maintained by brother-sister matings for > 12 years (5). Spontaneous tumors arising in the $CD8F_1$ female mice were transplanted by trocar fragments into $CD8F_1$ males as the first-generation transplants. Tumor-bearing female and non-tumor-bearing male mice were supplied to us by the Catholic Medical Center of Brooklyn and Queens, Inc, NY.

Tumor growth studies with the first-generation transplant involved the sc implantation by trocar of fragments from spontaneous tumors into the axillary region of recipient male mice. A single donor tumor was used for each experimental group as was recommended by Martin et al (6). Tumor growth was followed by caliper measurement of two perpendicular diameters. Tumor weight (mg) was calculated from mm measurements

$$\frac{\text{length} \times \text{width}^2}{2}$$

and tumor growth data were fitted by a Gompertz equation as previously described (7,8).

In three experiments, cells from each of three spontaneous donor tumors were dispersed mechanically (without enzymatic treatment), suspended, counted in a hemocytometer, and diluted to provide implant sizes of 10^7 or 10^8 cells and $\log_{10}$ dilutions thereof. Those cell suspensions were implanted sc. In one of the experiments brain tissue was added to each implant in an effort to improve the tumor take-rate. Both tumor growth and host mortality were observed to determine their relationships to tumor implant size.

Thymidine Studies

Tritiated thymidine (^{3}H-TdR, 6.7 curies/mmol) was injected ip at a dose of 2 microcuries/g of body weight for cell cycle studies or 10 microcuries/g of body weight for measurement of thymidine indices (TI). All injections were made between 8:00 and 9:00 AM and mice were killed 1 hour later for TIs or at the appropriate time for points on the percent labeled mitoses (PLM) curve. Both TI and PLM data were obtained on the first-generation transplants of each donor tumor.

Sample Preparation, Autoradiography, and Data Analysis

Tumors were harvested, preserved in 10% buffered formalin, and embedded in paraffin as previously described (8). Sections were cut at 4 microns, deparaffinized, treated with 1 N HCl for 1 minute at 60°C, and washed in distilled water. Slides were then dipped in Ilford K2 Emulsion (diluted 1:1 with distilled water) at 46°C. Emulsion-covered slides were stored with a drying agent at 4°C for 2 or 4 weeks (after ^{3}H-TdR was given at 10 microcuries/g of body weight) for measurement of the TIs and for 4 or 8 weeks for measurement of the PLM data (after ^{3}H-TdR was given at 2 microcuries/g of body weight). The emulsion-covered slides were developed in Kodak D19 Developer at 20°C for 4 minutes and stained with hematoxylin and eosin (8). Labeled cells were defined as those cells with 1 grain/cell in excess of the local background. Duplicate slides were evaluated for each exposure period by at least two investigators. Three thousand cells were scored on each slide for measurement of TIs and 200–400

TABLE 1.—Comparison of median day of host death and time required for tumor to reach 0.5 g from an sc implanted fragment: first-generation transplants of CD8F$_1$ mammary tumors

Experiment No.	No. of mice	Median day of death	Range	SD*	Median day to 0.5 g	Range	SD*
1450 D1(27)	10	53	34–97	20.5	17.8	14–29	4.8
1479 D1	9	58	42–>83	17.2	18.6	17–21	1.2
1450 G1	10	56.5	48–65	5.5	20.1	15–26	3.6
1479 C1	10	48	39–>74	11.4	22.3	20–25	1.8
1479 A1	9	57	34–68	11.5	28.1	22–36	4.5
1450 F1	10	71	46–115	22.4	28.4	22–36	4.8
1450 D1(1)	10	69.5	46–76	9.8	36.7	31–46	5.0
1450 A1	19	72	44–>133	24.1	39.4	24–78	14.7
1479 B1	10	63	34–>115	26.3	43.2	24–80	18.0
1465 C1	9	83	38–127	30	49.1	26–75	16.4
1450 J1	20	129	100–>146	15.2	66.5	100–>146	14.4

*SDs are included as a guide to the variability but may overestimate this variability if the death pattern or time to 0.5 g did not follow a normal distribution.

mitotic figures per slide were scored for the PLM curves. PLM data from the autoradiographs exposed for 8 weeks from first-generation transplants of four spontaneous donor tumors were pooled for analysis by the computer model of Steel and Hanes (9).

RESULTS

Tumor Growth

The consistency of tumor growth from experiment to experiment is an important factor in interpretation of therapeutic trials and table 1 lists the median days of host death and the median times required for tumors to reach 0.5 g (data from ten experiments). In addition, ranges and SDs are listed. Each group shown was a control for a chemotherapy trial and those mice were treated with diluent only. It can be seen from table 1 that among the 11 groups there was more than a twofold variation in the median day of death and nearly a fourfold variation in the median time required for tumor fragment implants to reach 0.5 g. A direct relationship could be seen between the median day of host death and the median time required for tumor implants to reach 0.5 g. Moreover, there was a tendency for the later-developing tumors to have larger SDs. That is, there was more variability in the time required for those late-developing tumors to reach 0.5 g and to kill the host. There was also greater variability in ten of the 11 experiments in the median day of death than in the time required to reach 0.5 g.

Among a number of possible factors that might influence the time required for tumor development is the cell viability, ie, the number of viable cells per unit mass of the spontaneous donor tumor selected for implantation. This view seems plausible since a single but different donor tumor was used for each experiment (table 1), and since tumors were transplanted as fragments without any prior attempt to determine cellularity or viability. The existence of a direct relationship between the number of cells implanted sc and the time required for tumors to reach 0.5 g (fig 1A) or to kill the host (fig 1B) also lends credence to that possibility.

Another possible factor that might influence the observed variability of first-generation tumor behavior could be donor tumor growth rates. To determine whether the growth characteristics of the spontaneous tumor might be used to predict or select the growth characteristics of transplanted tumors, the following experiment was performed. The growth of five spontaneous tumors was followed from the time the tumor-bearing mice were received until the tumors reached 3–4 g. At this time, each spontaneous tumor was used to implant fragments into ten CD8F$_1$ males and the growth of each of these tumors was followed until death of the host or at least 85 days. Growth data for individual tumors were fitted by a Gompertz function for calculation of the mass doubling time, and the median doubling time for each group of tumors is shown in table 2. Growth curves and associated data are shown in figure 2. Growth of the spontaneous tumors at 1.0 and 3.0 g was still highly variable, somewhat in contrast to the report of Anderson et al (10). There is little indication of a direct relationship between growth characteristics of the spontaneous donor tumor and either the growth characteristics or time of appearance of the transplanted tumors (table 2). Mice bearing transplants from the most rapidly growing spontaneous tumor survived for the longest period of any of the five groups. In four of the five groups, the doubling time of the transplanted tu-

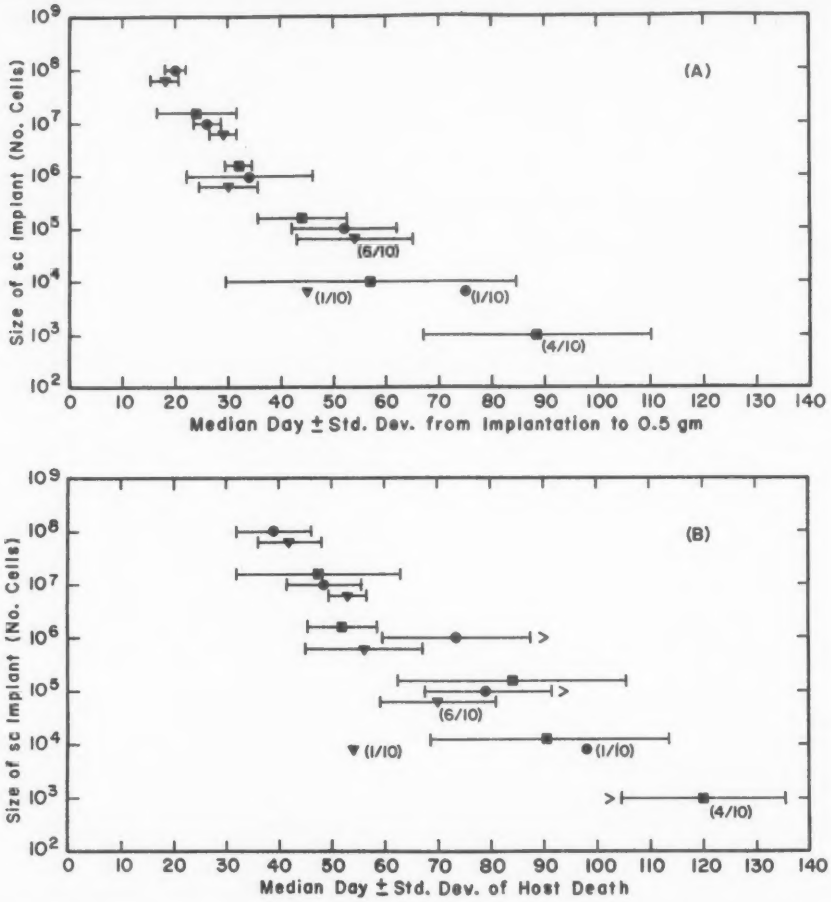


FIGURE 1.—First-generation transplants of CD8F$_1$ mammary tumors. Different symbols represent separate experiments. Brain tissue was added to the cells represented by ■. Nos. in parentheses = tumor incidence when < 10 of 10.

mors was shorter than for the corresponding donor tumor. In the fifth group, the opposite was true.

A mean or median tumor doubling time related to days postimplant of the first-generation tumor is almost meaningless in view of the highly variable time required for these tumors to reach 100 mg. Under these conditions, each data point may include tumor weights for both early and advanced tumors which results in a growth curve that does not well-represent any of the tumors. To compensate for this variation in time of appearance, we adjusted growth data for 70 transplanted tumors (ten from each of seven donor tumors) so that Day 0 became day of appearance and time was relative to the time of appearance. These data were then fitted by a Gompertz function and the resulting growth curve and tumor mass doubling time data are shown in figure 3. Gompertz-fitted curves for the adjusted data for the groups of ten mice with the earliest and latest median day of appearance (for these seven groups) are also shown for comparison.

Growth Data for Thymidine Studies

It would have been desirable to obtain growth data on representative first-generation tumors from each group used for thymidine studies but this was not feasible due to the limitation in number of transplants that could be made from each spontaneous tumor. An estimate of the approximate growth rates can be obtained from the time required for tumors in each group to reach the size range chosen for the PLM studies. Tumors were selected for the PLM curves by measuring tumors

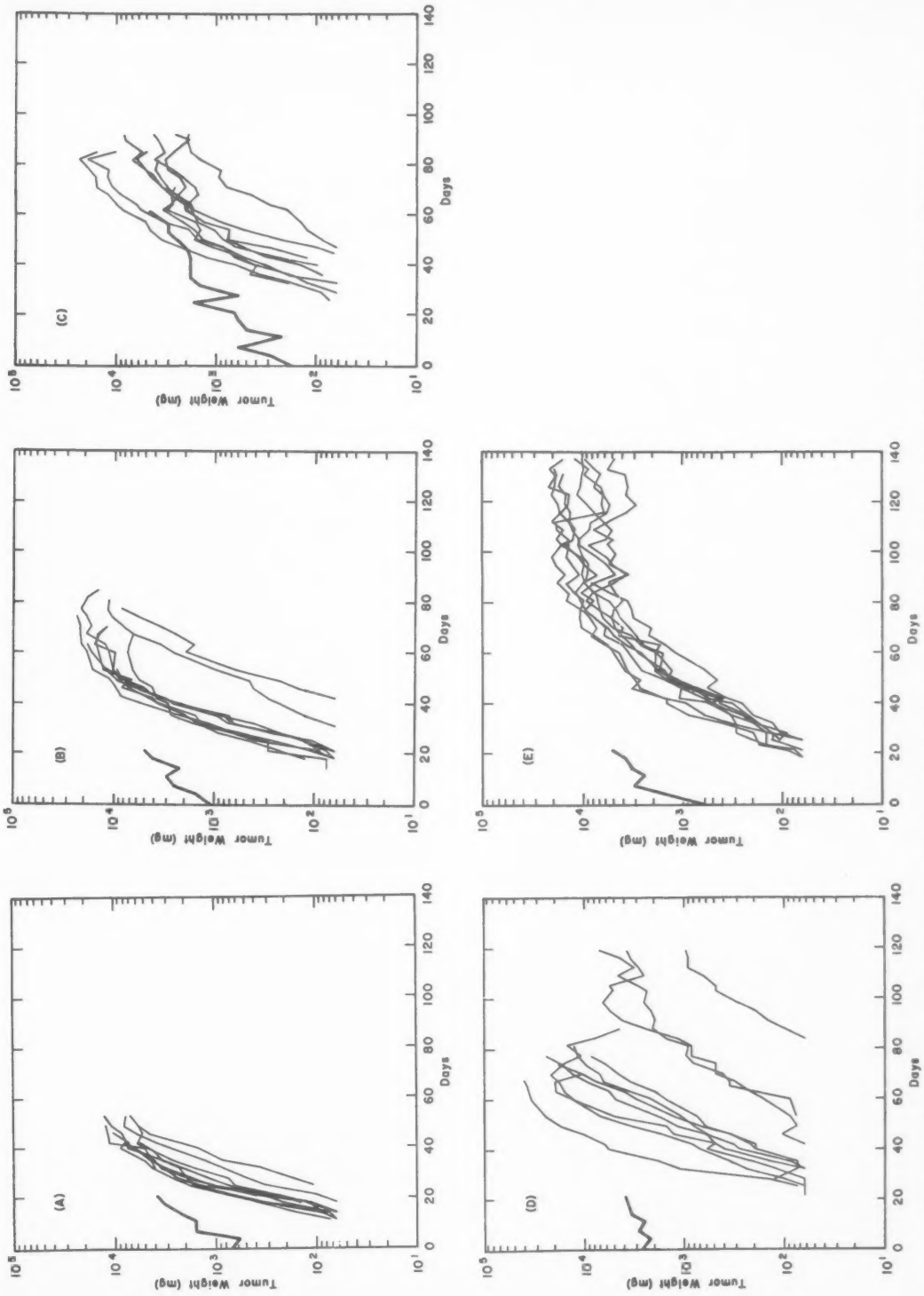
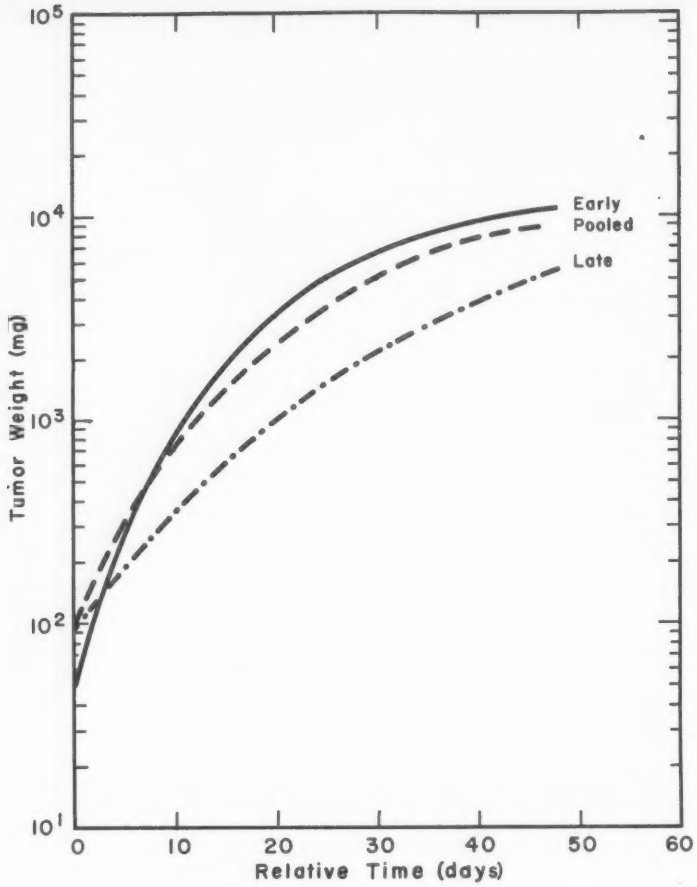


FIGURE 2.—Growth curves for spontaneous mammary adenocarcinomas (—) from the time the tumor-bearing mice were received until the tumors were used to implant male CD8F$_1$ mice with tumor fragments. These first-generation transplants (—) were followed until death of the host or for > 80 days. The scale is days postimplant for first-generation transplants or days from receipt of the female mice bearing spontaneous tumors.



Tumor Weight (mg)	Tumor Doubling Times (Days) Early	Late	Pooled Data*
	1450 D1	1465 C1	
10	1.4	3.5	1.9
50	1.8	4.3	2.4
100	2.0	4.8	2.8
500	3.1	6.7	4.1
1000	3.9	8.1	5.1
3000	6.8	12.0	8.7
5000	11.0	15.0	13.0

*Pooled data from 75 first generation transplants from 7 donor tumors.

FIGURE 3.—Gompertz-fitted growth curves for 7 groups of tumors (10 each). — = group of 10 mice with earliest median day of tumor appearance; —.—.— = group of 10 mice with latest median day of tumor appearance; — — — = pooled data for 7 groups. Tumor doubling times were obtained from tangents to the Gompertz-fitted curves.

TABLE 2.—Relationship between growth of spontaneous mammary adenocarcinomas in $CD8F_1$ mice and the first-generation transplants of these tumors

Tumor weight (mg)	Tumor mass doubling times and other biologic data (days)									
	No. 49A		No. 38A		No. 85		No. 8A		No. 39B	
	Spontaneous	Transplanted*	Spontaneous	Transplanted*	Spontaneous	Transplanted*	Spontaneous	Transplanted*	Spontaneous	Transplanted*
100	6.1	2.6	4.2	2.9	10.7	3.1	28.5	5.1	1.1	4.0
500	6.9	3.6	6.1	3.7	13.0	4.3	28.6	5.8	2.0	6.4
1000	7.3	4.1	7.4	4.3	14.3	7.2	28.6	6.0	2.9	8.4
3000	8.0	5.7	11.7	6.3	17.0	10.3	28.7	6.6	11.5	12.6
Median day for transplanted tumors to reach 100 mg		15.1		22.8		36.7		34.3		26.7
Median day of death for transplanted tumors		50.0		73.0		90.0		82.0		>134.0

*Growth data for individual transplanted tumors were fitted by a Gompertz function and doubling times were calculated for the designated tumor mass. The median value for the doubling time at each mass for all (usually 10) transplanted tumors in each group is shown in the table.

in each group of first-generation transplants from four donor tumors daily Monday through Friday until individual tumors fell within a range of 1–4 g of calculated weight (harvested tumor weights shown in fig 4 exceeded 4 g in two instances). At this time the tumor-bearing mouse was removed for injection of ^{3}H-TdR and subsequent study. Sufficient numbers of first-generation tumors from donor tumor No. 352 fell within the designated range by Day 24 (fig 4). No tumors transplanted from No. 353 were within the weight range until Day 37. These data only serve as an indication of the relative times required for the transplants from the four spontaneous tumors to reach a given range of calculated tumor mass.

Thymidine Studies

TIs of first-generation tumors as a function of time postimplant and tumor mass are shown in figure 4. The observed TIs are similar in each of the four groups of tumors and no differences related to donor tumor are apparent. These data are consistent with a slight decline in TI with time postimplant but the evidence is less convincing for a decline with tumor mass. Twenty percent to 35% of the cells were labeled in small tumors and 15%–30% in large tumors. One 100-mg tumor had a TI of only 10%. One mouse bearing a first-generation implant (39B) used for growth studies (fig 2) was injected with ^{3}H-TdR (10 microcuries/g of body weight) on Day 137 to determine whether these tumors might be characterized by a low TI (and a low proliferative rate). The tumor weighed 3.6 g and the TI was 0.20. Histologic study confirmed that the tumor was a poorly differentiated adenocarcinoma.

PLM data are shown in figure 5 and donor tumors are identified by symbol. Data were pooled for the computer analysis in view of the similarity of the four groups. The computed curve and cell cycle parameters are included in figure 5. The second wave is poorly defined and the computed curve does not appear to well-describe the data in this area. Alternatively, a hand-drawn curve connecting the mean values with the T_c and T_s calculated from 50% intercepts would yield parameters similar to the mean values obtained from the computer analysis.

DISCUSSION

Both the growth data for the spontaneous tumors and the first-generation transplants are well-described by a Gompertz function. Retardation of growth ranges from minimal (spontaneous tumor 8A, table 2) to extensive (spontaneous tumor 39B, table 2) in individual spontaneous as well as individual transplanted tumors. The acceleration of growth rate for 1-g transplanted tumors by Anderson et al (10) reflects the increase in tumor mass accumulated per unit time for larger tumors that is apparent when growth data are plotted on linear-linear coordinates and is not in conflict with the decrease in tumor mass doubling time described by the Gompertz function.

Studies of the growth behavior and lethality to the host of first-generation transplants of spontaneous mammary adenocarcinoma of $CD8F_1$

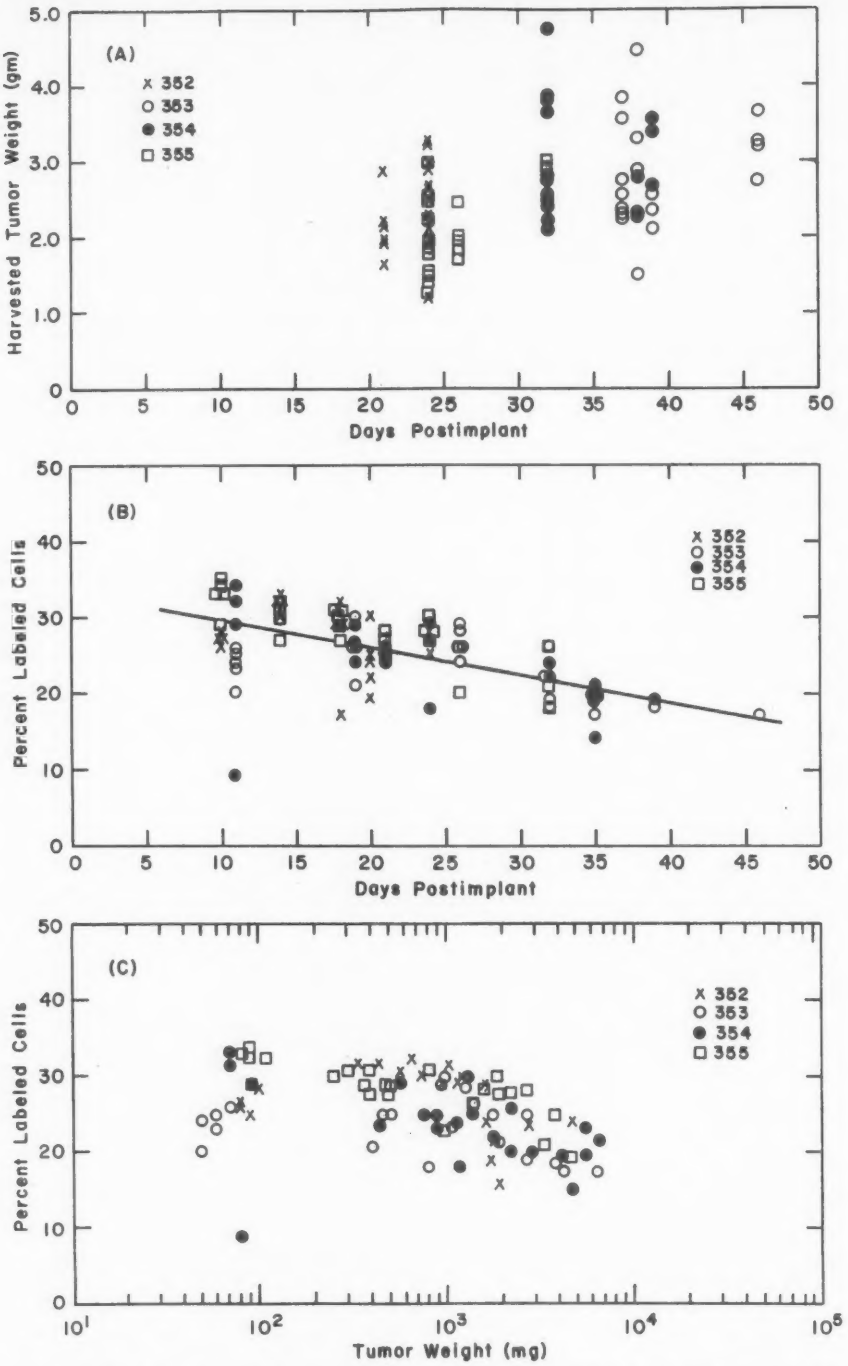


FIGURE 4.—Days postimplant when first-generation transplanted tumors from Nos. 352, 353, 354, and 355 reached the calculated 1–4-g weight range (harvested tumor weights exceeded 4 g in 2 instances) (top). Pulse TIs of first-generation transplants of 4 spontaneous tumors plotted as a function of days postimplant (center) or tumor mass (bottom). Data were obtained from autoradiographs exposed for 2 wks. Mean TI at about 100 mg = 27.7; mean TI at about 5000 mg = 20; overall mean = 27.

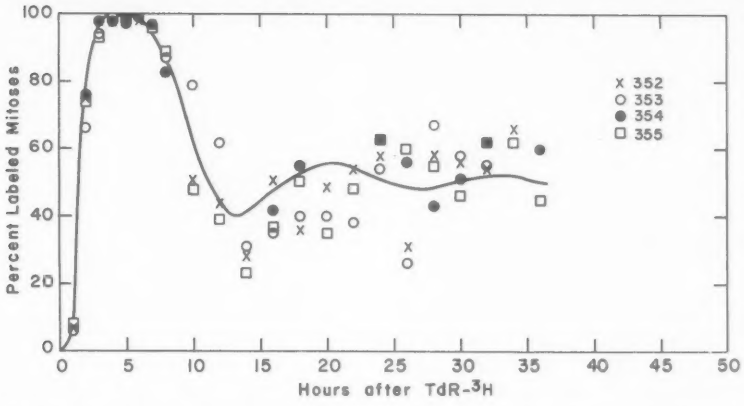


FIGURE 5.—PLM data for first-generation transplants of the 4 spontaneous tumors. Data were obtained from autoradiographs exposed for 8 wks. The curve and cell cycle parameters were obtained from the computer analysis by Dr. G. G. Steel.

Cell cycle parameters	Values from analysis (hrs)	
	Mean	Median
T_c	20.3	15.6
T_s	9.5 ± 2.9	9.1
T_{G1}	9.3 ± 20.8	3.5
T_{G2}	1.5 ± 0.6	1.4

mice revealed a twofold to fourfold variation in the time required for sc implanted tumor fragments to attain a weight of 0.5 g and in the time required for those tumors to kill the host.

Further, the ranges of those two parameters increased as the median or mean values increased. In experiments where $\log_{10}$ dilutions of counted numbers of cells (10^8, 10^7, 10^6, etc) were implanted sc, the greatest ranges in times required for those implants to grow to a given size and to kill the host were observed in those groups that received the smallest implants. This is consistent with observations previously made by Skipper and Schabel[5] with a variety of other transplantable tumors. A low order of tumor cell viability in the donor tumor may be one factor that contributes to the relatively late tumor appearance observed in some experiments following sc implantation of tumor fragments, but low cell viability is not consistent with the kinetic parameters found in those tumors associated with slow tumor growth (figs 4 and 5). A difference in cell viability should be evident in the comparison of TIs of tumor populations with similar cell cycle characteristics, ie, intact, but nonproliferative cells would increase the percentage of unlabeled cells and decrease the TI. No evidence for this was seen when the TIs of early- and late-appearing tumors were compared in figure 4. The TIs for these tumors are variable but the ranges overlap; no significant differences were observed. In addition, the TI obtained on one tumor from the growth study (tumor 39B) at Day 137 postimplant would not be consistent with a growth fraction low enough to account for the observable growth characteristics of these tumors. These data would indicate that the measured changes in tumor mass do not necessarily reflect the kinetic behavior of the cell population within the tumor.

The mean T_c is 20.3 with a median T_s of 9.5 ± 2.9 hours. The length of G_1 is highly variable according to this analysis with a mean of 9.3 ± 22.8 hours. Two points on the PLM curve, at 10 and 12 hours, appear to be somewhat out of line and might be indicative of some variation in S phase related to donor tumor No. 353, but the remainder of the data from this study did not support an assumption of difference, so the data were pooled. Omission of the two points (10 and 12 hours) from the analysis made only minimal differences in the results.

The PLM studies were planned for tumors in the 1–4-g range with the hope that cell cycle data might be obtained simultaneously on the primary tumor and on lung metastasis (10). Autoradiographs of lung sections were processed for every mouse but foci of identifiable tumor cells were found only occasionally and very few foci con-

[5] Skipper HE, and Schabel FM, Jr. Personal communication.

tained sufficient numbers of cells to provide statistically reliable data. These data were too scant to give any estimate of the relative kinetic parameters in the two tumor sites.

The results of these thymidine studies indicate that the cell cycle parameters and TIs of the transplanted tumors do not vary in relation to the donor tumor or to the growth characteristics of the transplanted tumors. This would lead to speculation that the considerable variability in day of appearance or growth might result from the rate of cell loss or cell death.

First-generation transplants of mammary adenocarcinomas in $CD8F_1$ mice usually grow more rapidly than the spontaneous donor tumor but these results do not indicate that selection of a fast- or slow-growing spontaneous $CD8F_1$ tumor for transplant will guarantee similar growth characteristics in the first generation of transplanted tumors. Other factors, such as the antigenicity of the spontaneous tumor or some characteristic of the recipient mice (possibly age or immune status), may be responsible for the variation in growth characteristics between tumors implanted from different spontaneous tumors.

REFERENCES

1. WEXLER H, MINTON JP, and KETCHAM AS. A comparison of survival time and extent of tumor metastases in mice with transplanted, induced, and spontaneous tumors. Cancer 18:985–994, 1965.
2. WEXLER H, ORME SK, and KETCHAM AS. Biological behavior through successive transplant generations of transplantable tumors derived originally from primary chemically induced and spontaneous sources in mice. J Natl Cancer Inst 40:513–523, 1968.
3. SCHOLLER J, PHILIPS FS, STERNBERG SS, ET AL. A comparative study of chemotherapeutic agents in spontaneous mammary adenocarcinomas of mice and in transplants of recent origin. Cancer 9:240–251, 1956.
4. SCHABEL FM, JR. Concepts for systemic treatment of micrometastases. Cancer 35:15–24, 1975.
5. STOLFI RL, MARTIN DS, and FUGMANN RA. Spontaneous murine mammary adenocarcinoma: model system for evaluation of combined methods of therapy. Cancer Chemother Rep 55:239–251, 1971.
6. MARTIN DS, FUGMANN RA, STOLFI RL, ET AL. Solid tumor animal model therapeutically predictive for human breast cancer. Cancer Chemother Rep Part 2, vol 5(1):89–109, 1975.
7. SIMPSON-HERREN L, and LLOYD HH. Kinetic parameters and growth curves for experimental tumor systems. Cancer Chemother Rep 54:143–174, 1970.
8. SIMPSON-HERREN L, SANFORD AH, HOLMQUIST JP, ET AL. Ambiguity of the thymidine index. Cancer Res 36:4705–4709, 1976.
9. STEEL GG, and HANES S. The technique of labelled mitoses: analysis by automatic curve-fitting. Cell Tissue Kinet 4:93–105, 1971.
10. ANDERSON JC, FUGMANN RA, STOLFI RL, ET AL. Metastatic incidence of a spontaneous murine mammary adenocarcinoma. Cancer Res 34:1916–1920, 1974.

Analysis of Methotrexate and 7-Hydroxymethotrexate by High-Pressure Liquid Chromatography [1,2]

Jeffrey L. Wisnicki, William P. Tong, and David B. Ludlum [3,*]

SUMMARY

The use of high-dose methotrexate (MTX) therapy in cancer chemotherapy has intensified the need to monitor the purity of this drug. A high-pressure liquid chromatographic method, which utilizes ion-pairing on a μ-Bondapak C_{18} column, has been developed for this purpose. This method provides an efficient and highly sensitive method for detecting impurities in commercially available MTX. As has been demonstrated previously, patients receiving high-dose MTX therapy metabolize some of this drug to 7-hydroxymethotrexate (7-hydroxy-MTX), a derivative which is considerably less soluble than MTX itself. Consequently, 7-hydroxy-MTX may contribute to the renal toxicity commonly associated with high-dose therapy. An assay similar to the one described above is also applicable to this problem and can be used to assay MTX and 7-hydroxy-MTX directly in patients' urine.

[Cancer Treat Rep 62:529–532, 1978]

High-dose methotrexate (MTX) therapy (> 50 mg/kg) followed by citrovorum factor treatment has been effectively employed in the adjuvant chemotherapy for a variety of neoplasms, particularly osteogenic sarcoma (1,2). In view of the extremely high doses of MTX which are now being given, the presence of contaminants is of great concern and their analysis is of compelling importance.

When MTX is administered in high doses, some of the drug is metabolized to 7-hydroxymethotrexate (7-hydroxy-MTX) (3). This metabolite has considerably less aqueous solubility than MTX itself and may be partly responsible for the renal toxicity which is a common complication of high-dose therapy (3–5).

We report here the development of a high-pressure liquid chromatographic (HPLC) separation which demonstrates the presence of 21 impurities in a clinically used sample of MTX. A similar chromatographic analysis can be used as a sensitive and rapid assay for MTX and 7-hydroxy-MTX in patients' urine.

MATERIALS AND METHODS

A sample of MTX in current clinical use (lot No. BV-76-227), packaged by Ben Venue Laboratories, Inc, and prepared by the method of Piper and Montgomery (6), was obtained from Dr. Herbert Kaizer of The Johns Hopkins Oncology Center (Baltimore, Md). 7-Hydroxy-MTX, purified from the urine of rhesus monkeys receiving high-dose MTX, was the gift of Dr. David G. Johns of the Division of Cancer Treatment, NCI (Bethesda, Md). Markers of possible impurities included 4-amino-4-deoxy-N^{10}-methylpteroic acid (APA), 2-amino-4-hydroxy-N^{10}-methylpteroyl-glutamic acid (methopterin) (both from Lederle Laboratories), and 4-aminopteroyl-glutamic acid (aminopterin) (Sigma Chemical Co).

Urine samples obtained from pediatric patients receiving high-dose MTX therapy were kindly supplied by Dr. Kaizer. Specimens of urine were obtained from a female patient with histiocytosis and a male patient with osteogenic sarcoma and kept frozen at −20°C. These patients had received high-

[1]Received Oct 13, 1977; revised Jan 26, 1978; accepted Jan 31, 1978.

[2]Supported by Public Health Service grants CA-20129 and CA-20292 from the National Cancer Institute (NCI), National Institutes of Health, Department of Health, Education, and Welfare.

[3]Department of Pharmacology and Experimental Therapeutics, Albany Medical College, NY.

Reprint requests to: David B. Ludlum, PhD, MD, Department of Pharmacology and Experimental Therapeutics, Albany Medical College, Albany, NY 12208.

dose MTX by infusion over a 6-hour period as part of an adjuvant chemotherapy program. The MTX used in the treatment of the osteogenic sarcoma patient was from the same lot as the drug analyzed for impurities.

HPLC was performed with a Milton Roy 5000-psi minipump equipped with a Laboratory Data Control pulse damper (model 709). Column effluent was monitored with a Laboratory Data Control ultraviolet (UV) detector at 254 nm. Analyses were conducted on a μ-Bondapak C_{18} analytic column (4.0-mm internal diameter, 30 cm long, Waters Associates) and preparative scale work for the collection of MTX impurities was carried out on a μ-Bondapak C_{18} preparative column (7.0-mm internal diameter, 30 cm long). Anion exchange chromatography was performed on a Reeve Angel Partisil-10 SAX column (4.6-mm internal diameter, 25 cm long).

Ten-microliter samples of MTX at approximately 1.4 mg/ml each were injected on the μ-Bondapak C_{18} analytic column and eluted with 5 mM tetrabutylammonium phosphate, pH 7.5 (PIC Reagent A, Waters Associates)/acetonitrile, 80/20 (vol/vol). Flow rates were kept constant at 0.45 ml/minute and detector attenuation was set at 0.04 ODU full scale. The same solvent was used at a flow rate of 1.0 ml/minute for the μ-Bondapak C_{18} preparative scale column. A 250-μl sample of MTX solution was injected on this column and 1-minute fractions were collected.

All urine specimens were filtered through a 0.45-μ Millipore filter prior to injection. Again, 10-μl samples were used for analyses and 250-μl samples were used for collection of MTX and 7-hydroxy-MTX for spectroscopic studies. Urine samples were eluted with 5 mM tetrabutylammonium phosphate, pH 7.5 (PIC Reagent A, Waters Associates)/methanol, 70/30 (vol/vol). The amounts of MTX and 7-hydroxy-MTX in the urine were calculated from peak areas corrected by the molar extinction coefficients at 254 nm of 16,500 and 10,000 for MTX and 7-hydroxy-MTX, respectively. Strong anion exchange chromatography of MTX and 7-hydroxy-MTX was carried out with an eluent of 50 mM $(NH_4)_2HPO_4$, adjusted to pH 6.5 with 10 M H_3PO_4, and pumped at a flow rate of 0.5 ml/minute.

UV spectra of markers were obtained on a Beckman Model DBG spectrophotometer in acid, neutral, and alkaline solutions. Spectra of collected MTX impurities were run on a Beckman Acta MVI spectrophotometer made available through the courtesy of Mr. Denis Kebabjian, NY State Police Laboratories.

RESULTS

Analysis of MTX Purity

The use of paired-ion chromatography improves the separation obtained on a μ-Bondapak C_{18} column over that obtained with an ordinary buffered solvent. A typical analysis of MTX used in the high-dose chemotherapy regimen is shown in figure 1. Twenty-one separate impurity peaks were detected which together amounted to approximately 6% of the total peak area. To show that these impurities were not being generated on the column, the MTX peak was collected and re-injected. On re-injection, it appeared as one sharp peak.

MTX itself appeared as peak 18. Impurities of APA, aminopterin, and methopterin which have been found in other samples of MTX have retention

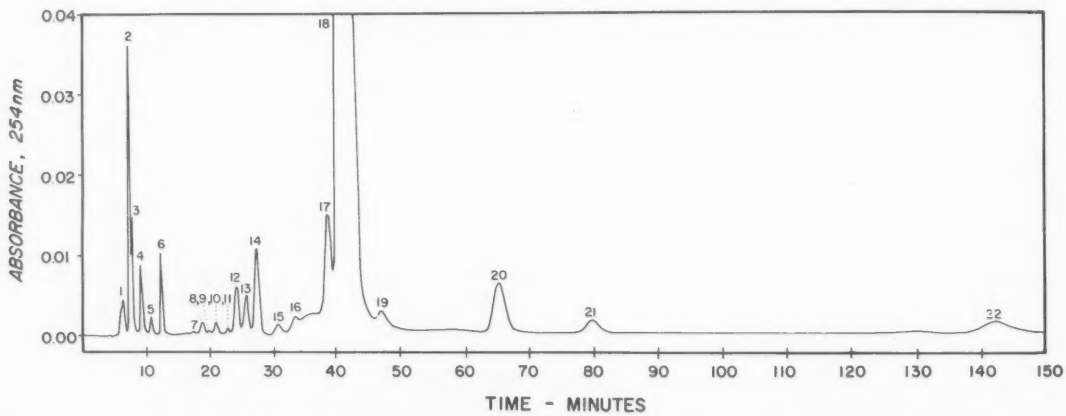


FIGURE 1.—Paired-ion HPLC of MTX on a μ-Bondapak C_{18} column. In addition to peak 18 (MTX), there are 21 other peaks representing contaminants.

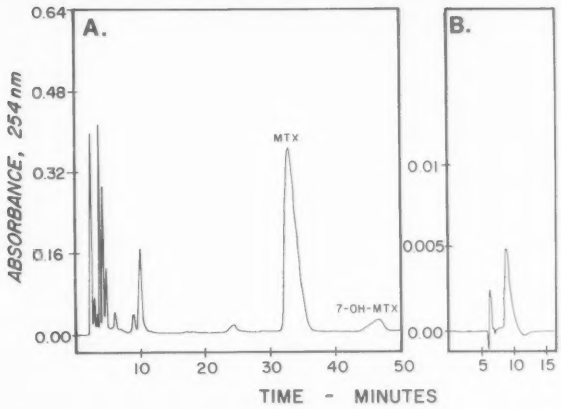


FIGURE 2.—A. Paired-ion HPLC of 24-hr urine sample from patients receiving high-dose MTX. B. Confirmation of identity of 7-hydroxy-MTX. Urinary 7-hydroxy-MTX collected from the μ-Bondapak C_{18} column was run on a strong anion exchange column. Retention time (9.0 mins) was the same as that for the known reference compound.

times corresponding to peaks 8, 14, and 17, respectively (7–9).

Further support for the identity of peak 17 was obtained by good agreement between the spectra for the collected impurity and methopterin. Scans of aminopterin resembled those of peak 14. In addition, spectral data for peak 2 correspond to those previously reported for an unidentified impurity in MTX, possibly an unconjugated 2,4-diaminopteridine (8). The amount of material collected from peak 8 was insufficient for scanning.

Assay for Urinary MTX and 7-Hydroxy-MTX

Urine samples from patients receiving high-dose MTX were analyzed directly on the μ-Bondapak C_{18} column. MTX and 7-hydroxy-MTX appeared with average retention times of 35 and 48 minutes, respectively (fig 2). These retention times corresponded to those obtained with reference material. To confirm the identity of the urinary MTX and 7-hydroxy-MTX, fractions containing the drug and its metabolite were collected. UV spectra of both peaks were in good agreement with those reported previously (5,10,11).

As further confirmation, a system using a strong anion exchange column was developed in which MTX and 7-hydroxy-MTX were resolved with retention times of 12.5 and 9.0 minutes, respectively. As shown in figure 2B, the peak corresponding to urinary 7-hydroxy-MTX isolated on a μ-Bondapak C_{18} column was found to have the correct retention time for 7-hydroxy-MTX when it was re-injected on the strong anion exchange column. Similarly, the peak for urinary MTX from the μ-Bondapak C_{18} column had the correct retention time of 12.5 minutes on the anion exchange column.

Chromatography of MTX from the same lot used to treat one of the patients studied revealed that 7-hydroxy-MTX was absent in the original drug and is, therefore, a metabolic product. Analyses of a 24-hour urine specimen following MTX infusion from the patient with histiocytosis and a spot sample taken shortly after MTX infusion from the osteogenic sarcoma patient indicated that the percentages of drug excreted as 7-hydroxy-MTX were 10% and 0.9%, respectively.

DISCUSSION

The use of MTX at levels thousands of times higher (12) than those used previously makes careful analysis of the drug critically important because any impurities present would be administered in significant doses. Previous studies of MTX purity have included analyses with DEAE ion-exchange column chromatography (8,9) and paper electrophoresis (13). More recently, MTX has been analyzed on a reverse-phase column with a standard buffer (7). The increased sensitivity and resolution of this new assay coupled with the advantages of ease and rapidity offered by high pressure separation provide an improved means of monitoring MTX impurities.

MTX is apparently not significantly metabolized in man following the administration of conventional doses (14,15). However, it has been demonstrated that man and primates both excrete substantial quantities of 7-hydroxy-MTX in the urine when they are placed on the high-dose regimen (> 50 mg/kg) (3,5). Primates excrete 7-hydroxy-MTX when they are given doses as low as 6.5 mg/kg (16). Since monkeys that developed renal failure from high-dose MTX were found to have crystalline deposits within the tubules (3,5), it is believed that the precipitation of MTX and its less soluble metabolite may contribute to renal toxicity.

Chromatographic separation of MTX and 7-hydroxy-MTX has previously been achieved on DEAE columns (3,5). This procedure is time consuming and not convenient for rapid clinical monitoring of drug and metabolite levels. The reverse phase HPLC method reported here enables urine concentrations of both MTX and 7-hydroxy-MTX to be measured quickly and quantitatively.

The present work has also shown that HPLC with a strong anion exchange column can be used to separate MTX and 7-hydroxy-MTX in aqueous solution. However, anion exchange chromatography has

provided significantly less resolving power than paired-ion chromatography on μ-Bondapak C_{18}. The use of a μ-Bondapak C_{18} column also permits filtered urine samples to be injected directly without serious damage to the column. Extraction procedures are avoided and the assay for MTX and 7-hydroxy-MTX can be completed in < 1 hour.

The assay for urinary MTX and 7-hydroxy-MTX reported here provides for an effective way of monitoring MTX and 7-hydroxy-MTX excretion, and should be useful in helping to prevent the development of renal toxicity.

REFERENCES

1. JAFFE N, FREI E III, TRAGGIS D, ET AL. Adjuvant methotrexate and citrovorum-factor treatment of osteogenic sarcoma. N Engl J Med 291:994–997, 1974.
2. DJERASSI I, and KIM JS. Methotrexate and citrovorum factor rescue in the management of childhood lymphosarcoma and reticulum cell sarcoma (non-Hodgkin's lymphomas). Cancer 38:1043–1051, 1976.
3. JACOBS SA, STOLLER RG, CHABNER BA, ET AL. 7-Hydroxymethotrexate as a urinary metabolite in human subjects and rhesus monkeys receiving high-dose methotrexate. J Clin Invest 57:534–538, 1976.
4. STOLLER RG, JACOBS SA, DRAKE JC, ET AL. Pharmacokinetics of high-dose methotrexate (NSC-740). Cancer Chemother Rep Part 3, vol 6(1):19–24, 1975.
5. JACOBS SA, STOLLER RG, CHABNER BA, ET AL. Dose-dependent metabolism of methotrexate in man and rhesus monkeys. Cancer Treat Rep 61:651–656, 1977.
6. PIPER JR, and MONTGOMERY JA. Preparation of 6-(bromomethyl)-2,4-pteridinediamine hydrobromide and its use in improved synthesis of methotrexate and related compounds. J Org Chem 42:208–211, 1977.
7. TONG WP, ROSENBERG J, and LUDLUM DB. Letter: Purity of methotrexate. Lancet 2(7937):719, 1975.
8. VALERINO DM. Letter: Methotrexate impurities. Lancet 2:1025, 1972.
9. GALLELLI JF, and YOKOYAMA G. Assay of methotrexate in the presence of its decomposition products and other folic acid analogs. J Pharm Sci 56:387–389, 1967.
10. SEEGER DR, COSULICH DB, SMITH JM, JR, ET AL. Analogs of pteroylglutamic acid. III. 4-Amino derivatives. J Am Chem Soc 71:1753–1758, 1949.
11. JOHNS DG, and LOO TL. Metabolite of 4-amino-4-deoxy-N^{10}-methylpteroylglutamic acid (methotrexate). J Pharm Sci 56:356–359, 1967.
12. DJERASSI I, KIM JS, and SHULMAN K. High-dose methotrexate-citrovorum factor rescue in the management of brain tumors. Cancer Treat Rep 61:691–694, 1977.
13. TISMAN G, and WINSTEIN WA. Letter: Methotrexate impurities. Lancet 1:1178, 1970.
14. JOHNS DG, HOLLINGSWORTH JW, CASHMORE A, ET AL. Methotrexate displacement in man. J Clin Invest 43:621–629, 1964.
15. HENDERSON ES, ADAMSON RH, and OLIVERIO VT. The metabolic fate of tritiated methotrexate. II. Absorption and excretion in man. Cancer Res 25:1018–1024, 1965.
16. KIMELBERG HK, BIDDLECOMBE SM, and BOURKE RS. Distribution and degradation of [^{3}H] methotrexate after intravenous and cerebral intraventricular injection in primates. Cancer Res 37:157–165, 1977.

Qualitative and Quantitative Toxicity of Single and Sequential Sublethal Doses of 5-Fluorouracil in BDF_1 Mice [1,2]

S. D. Harrison, Jr,* E. P. Denine, and J. C. Peckham[3,4]

SUMMARY

Qualitative and quantitative toxicity studies were conducted in BDF_1 mice after ip injection of 33, 66, 134, and 200 mg/kg of 5-fluorouracil (5-FU) in daily doses for 1, 2, 3, or 4 consecutive days. Groups of five mice from each schedule and dose level provided blood and selected visceral organs for hematologic and histologic evaluation on posttreatment Days 1, 3, 6, 10, 14, and 21. Comparable groups of five mice were blood donors for biochemical evaluation of pooled plasma samples. The results indicated the onset, severity, and duration of injury to target organs and characterized the relationship of sublethal toxicity to drug dose and frequency of administration. Marrow suppression was reflected in peripheral erythropenia, thrombocytopenia, and leukopenia and also in medullary erythropenia and granulocytopenia. A transient elevation of plasma LDH, loss of body weight, and appearance of microscopic lesions of the gastrointestinal mucosae were additional indices of toxicity. The BDF_1 mouse appears to provide a good qualitative and quantitative prediction of 5-FU toxicity, although the mouse apparently is quantitatively more sensitive than man.

[Cancer Treat Rep 62:533–545, 1978]

Experience accumulated with several animal species in a number of laboratories has provided continued support for the contention that the mouse is a useful model for preclinical toxicity studies of anticancer drugs (1–5). At least three important features recommend the mouse for these studies. Qualitative and quantitative indices of clinically relevant drug toxicity are identifiable and measurable in the mouse (1). Since an impressive array of spontaneous and transplantable tumors may be maintained in mice, drug effects may be studied in the mouse in the presence of neoplastic disease (4). Although the validity of extrapolating drug effects from mouse to man is not always predictable, maximum tolerated doses of anticancer drugs in the mouse are comparable to clinically acceptable doses based on body surface area (2,3). One purpose of the present study was to test further the premise that the features of sublethal drug toxicity observed in the mouse are qualitatively and quantitatively similar to dose-limiting toxicity in man.

In a previous study, we gave special attention to the recovery of vital, normal cell populations from drug-induced injury (1). We noted that mild anemia persisted for 42 days following single doses of methyl-CCNU (meCCNU) in BDF_1 mice. We also observed acute renal tubular necrosis, but whether the anemia and the renal toxicity were related was not clear. Anemia has been observed in patients treated with meCCNU, but renal toxicity has not been reported. If the mouse is to be a useful model of drug toxicity in man, greater similarity between the two species must be demonstrated. Accordingly, we have extended our investigations.

The toxicity and therapeutic effectiveness of 5-

[1] Received Oct 25, 1977; revised Jan 16, 1978; accepted Jan 19, 1978.

[2] Supported by contract N01-CM-57000 from the Division of Cancer Treatment (DCT), National Cancer Institute (NCI), National Institutes of Health, Department of Health, Education, and Welfare.

[3] Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Ala.

[4] We wish to acknowledge the assistance of Anne Cusic and the staff of the Preclinical Pharmacology Section who carried out the hematologic and clinical chemistry analyses. Dr. Harris H. Lloyd prepared the programs for analyzing and plotting our data, and Vergia Askew assisted in data management.

* *Reprint requests to:* Steadman D. Harrison, Jr, PhD, Preclinical Pharmacology Section, Southern Research Institute, 2000 9th Ave S, Birmingham, Ala 35205.

fluorouracil (5-FU) have been subjects of extensive study (6). 5-FU has had broad applicability in the treatment of neoplastic disease (6,7) since its synthesis and development (by Heidelberger et al [8]), and the clinical toxicity of this drug has been amply described (6,9–12). The toxicity of 5-FU is not cumulative, and recovery in man appears to be straightforward and complete within about 3 weeks. Moreover, the general utility of 5-FU in cancer treatment (6), particularly its recent use in highly effective drug combinations (7,13), has made it an attractive candidate for our studies. Consequently, we have carried out a qualitative and quantitative evaluation of the toxicity of single and sequential sublethal doses of 5-FU in BDF_1 mice.

MATERIALS AND METHODS

5-FU was obtained from the Developmental Therapeutics Program, DCT, NCI (Bethesda, Md). The drug was dissolved in physiologic saline and diluted to deliver 0.1 ml/10 g of body weight for injection into mice.

A total of 1600 male BDF_1 mice (Southern Animal Farms, Prattville, Ala) were used in this study. The mice, weighing 25–27 g each and in apparent good health, were randomly distributed into four groups of 400 mice each. Each group was subdivided into five treatment groups of 80 mice each. Each animal was housed in an individual stainless-steel cage and received Wayne Lab-Blox F6 (Allied Mills, Inc, Chicago, Ill) and water ad libitum. All animals were weighed prior to treatment.

Groups of 400 mice were treated with single daily ip doses of 5-FU for 1, 2, 3, or 4 consecutive days. Subgroups of 80 mice were dosed with 33, 66, 134, or 200 mg/kg which represent respectively, the estimated 0.16 LD10, 0.33 LD10, 0.67 LD10, and LD10 of a single dose of 5-FU. Doses were administered on the basis of individual body weights. Each fifth subgroup of 80 mice was dosed ip with drug solvent (physiologic saline) on the basis of body weight. On posttreatment Days 1, 3, 6, 10, 14, and 21 (last day of treatment equals 0), ten mice from each subgroup were individually weighed and killed for the study of the impact of and recovery from drug treatment on the formed elements of peripheral blood, liver, kidney, spleen, various levels of the gastrointestinal tract, bone marrow, and selected biochemical parameters. Five animals from each group of ten served solely as donors of pooled plasma for the latter aspect of the study. The remaining mice were held through 30 posttreatment days as toxicity controls.

When the mice were killed, whole blood was collected via cardiac puncture. Blood samples for hematology were collected in heparinized syringes and transferred into vials containing K_2-EDTA. Hematologic assessments included erythrocyte, leukocyte, platelet, differential leukocyte, and reticulocyte counts. The hemoglobin concentration and hematocrit determinations were made on each anticoagulated specimen. Femoral marrow was collected and evaluated as reported previously (1). Whole blood from the mice that served as donors for clinical chemistry studies was pooled in centrifuge tubes that had been rinsed with an aqueous solution of lithium heparin (1000 units/ml). After centrifugation (approximately 1000 × *g*, 10 minutes), plasma samples were collected for the determination of BUN (14), LDH (15), and SGPT (16). Samples of visceral organs, left femur, and sternum were collected and preserved in buffered formalin (pH 7). For qualitative and semiquantitative microscopic evaluation, these tissue samples were trimmed to a maximum thickness of 0.3 cm and embedded in Paraplast (Sherwood Medical Industries, St. Louis, Mo) using a Trimatic automatic tissue processor (Lipshaw Manufacturing Corp, Detroit, Mich). The samples were sectioned at 4–6 μm and stained with Harris' hematoxylin and eosin (17).

RESULTS

All experiments included concurrent lethality control groups that were observed for 30 posttreatment days for incidence of mortality. Cumulative mortality plots are presented in figure 1. Log probit plots of these and other[5] mortality data indicate that the LD10 for one, two, three, and four sequential daily doses of 5-FU is about 200, 162, 61, and 39 mg/kg/dose, respectively. Since only sublethal doses are clinically relevant, we have excluded from our analyses any effects produced by doses that were ultimately lethal. On this basis, we have analyzed data from treatment groups that received doses not $>$ 200 mg/kg (single dose), and 134 (qd × 2), 66 (qd × 3), and 33 (qd × 4) mg/kg.

Reticulocyte counts reveal that marrow production was suppressed within 2 days following the first dose of 5-FU (fig 2A). Probably because of the time required for maturation of circulating reticulocytes and release of preformed marrow reticulocytes after drug administration, the peripheral nadir did not occur until about 3 days after the first dose. This nadir persisted for 7 additional days in mice that received 200 mg/kg. Recovery was evident 14 days after the first dose. The duration of peripheral depression probably reflects the time required for marrow production to supply mature circulating

[5] Southern Research Institute. Unpublished data.

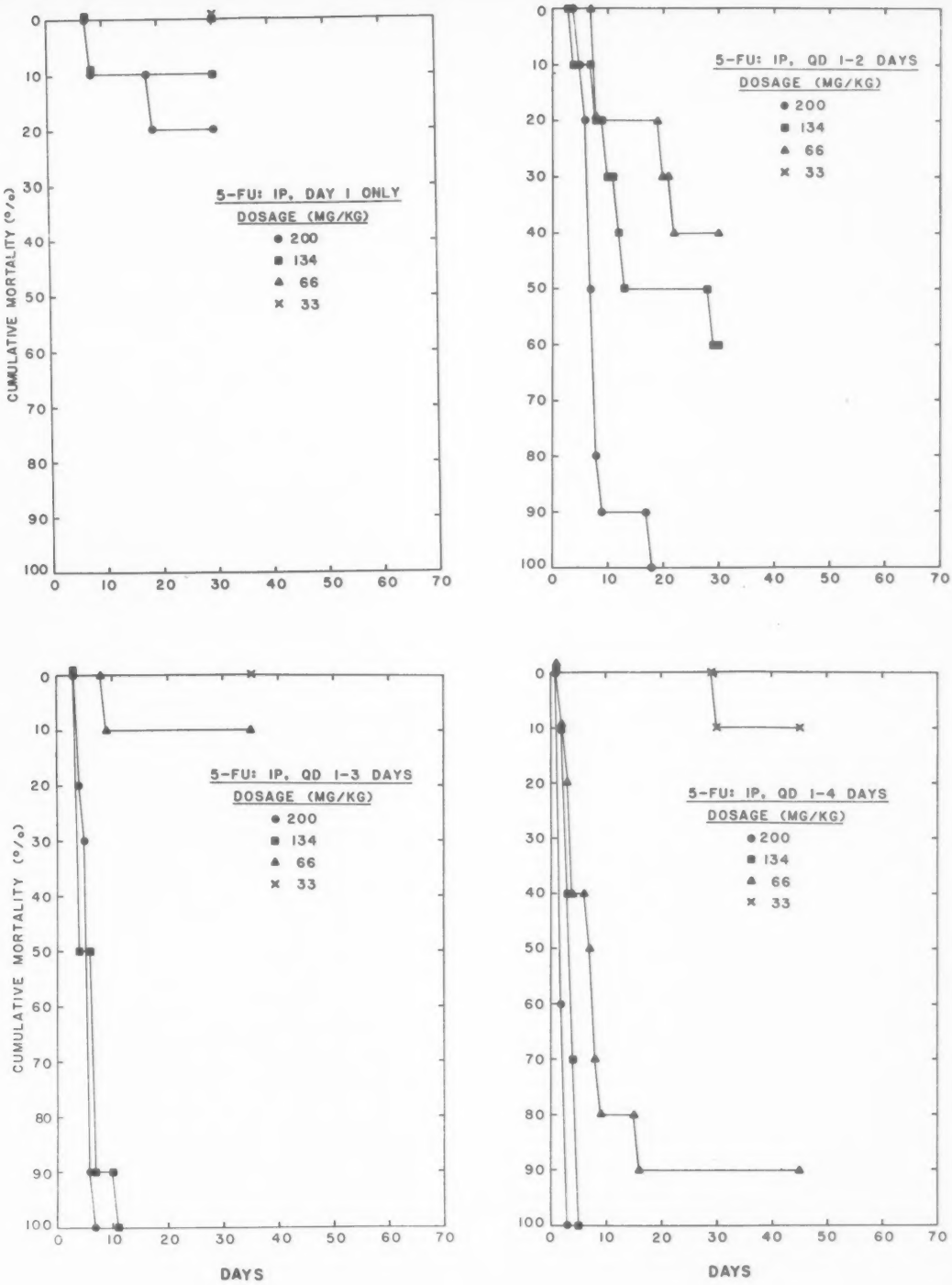


FIGURE 1.—Cumulative mortality of BDF_1 mice treated with 5-FU.

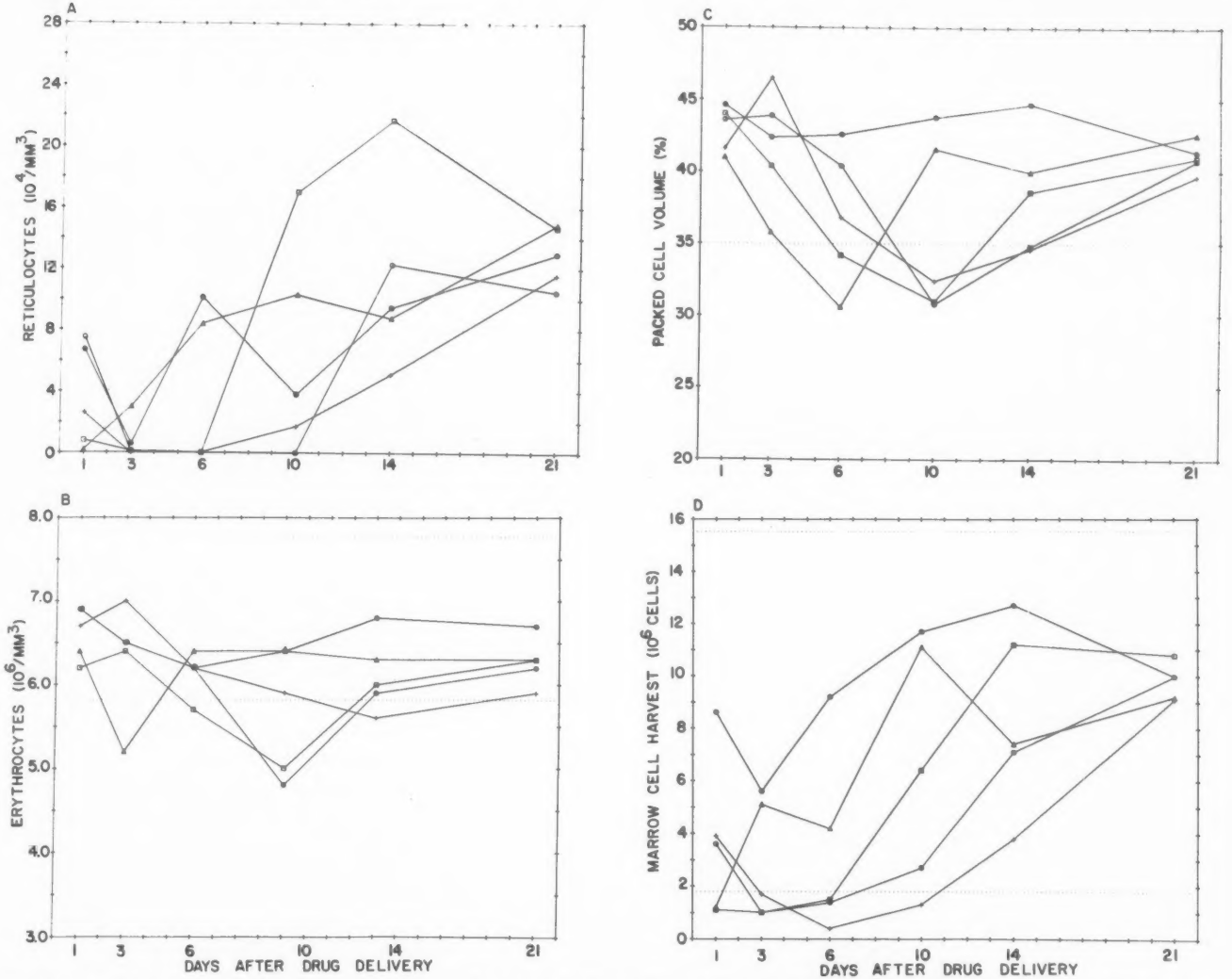


FIGURE 2.—Effects of single and sequential sublethal doses of 5-FU on reticulocytes (A), erythrocytes (B), packed cell volume (C), and total marrow cell harvest (D) in BDF_1 mice. Each point represents the mean of values from 5 individual mice. • = 33 mg/kg qd × 1; ○ = 200 mg/kg qd × 1; + = 134 mg/kg qd × 2; □ = 66 mg/kg qd × 3; and △ = 33 mg/kg qd × 4. Dotted lines = reference range, 97.5 and 2.5 percentile limits from the frequency distribution of data from 504 healthy male BDF_1 mice.

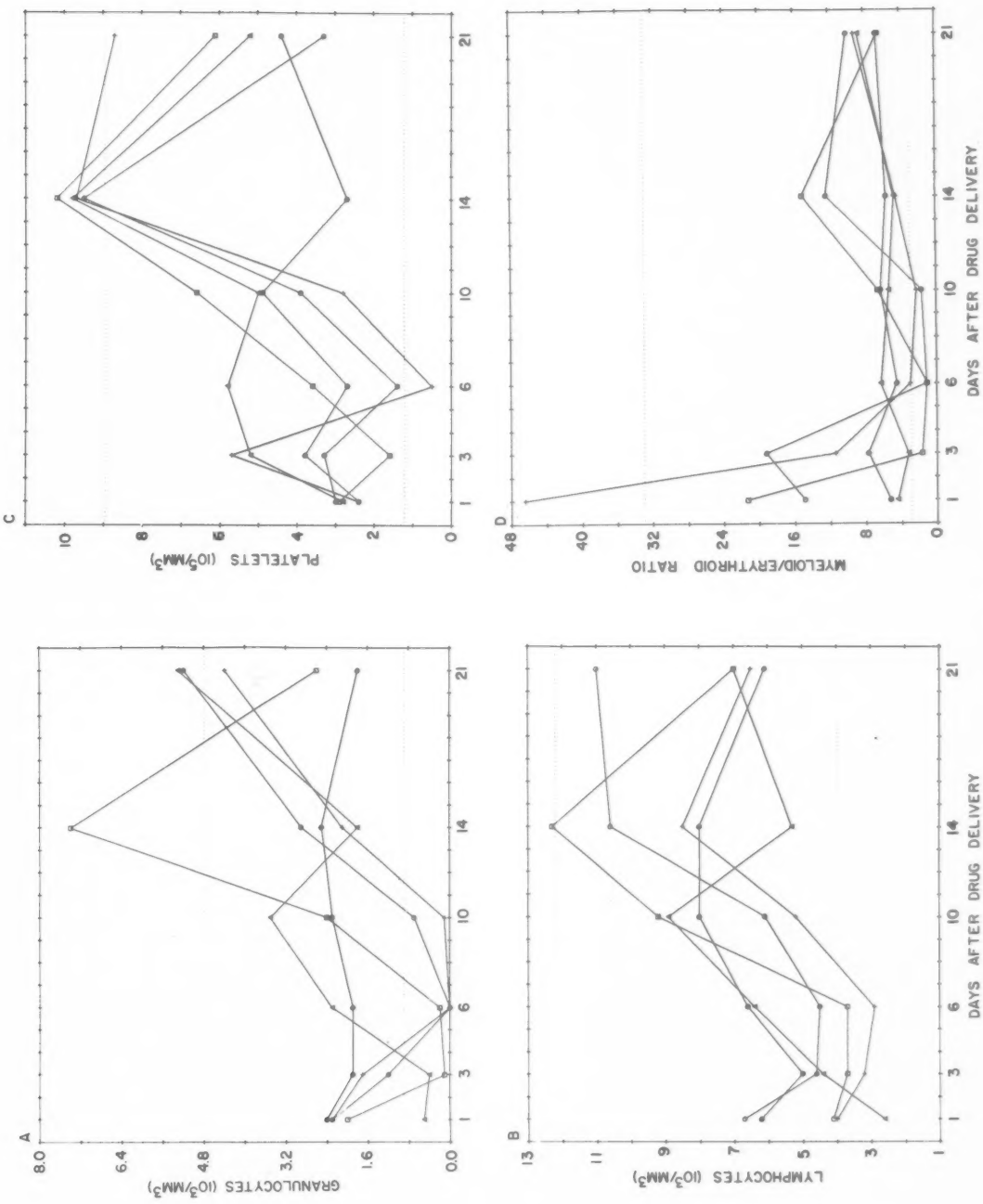


FIGURE 3.—Effects of single and sequential sublethal doses of 5-FU on granulocytes (A), lymphocytes (B), platelets (C), and M:E ratio (D) in BDF_1 mice. Each point represents the mean of values from 5 individual mice. ● = 33 mg/kg qd × 1; ○ = 200 mg/kg qd × 1; + = 134 mg/kg qd × 2; □ = 66 mg/kg qd × 3; and △ = 33 mg/kg qd × 4. Dotted lines = reference range, 97.5 and 2.5 percentile limits from the frequency distribution of data from 504 healthy male BDF_1 mice.

reticulocytes. The rate of marrow recovery is reflected by the dose-dependent return of reticulocyte counts to normal. Although the number of daily doses following the first dose had a predictable effect on host mortality (fig 1), the time required for recovery of reticulocytes and other cells was not increased by a second, third, or fourth dose if the schedule was sublethal (figs 2 and 3).

An erythrocyte nadir was observed on Day 10 posttreatment (fig 2B). The delay probably indicates the time between cessation of marrow activity and lysis of aged cells required to measurably reduce the numbers of circulating erythrocytes. A trend toward recovery was evident 11–16 days after the first dose; this corresponds to the time of marrow recovery indicated by reticulocyte counts. Packed cell volumes (fig 2C) paralleled erythrocyte counts.

Changes in the total marrow cell harvest (fig 2D) reflect the toxicity indicated by peripheral hematology. The earliest posttreatment reduction of harvested cells resulted from multiple-dose schedules. The highest total dose caused the most severe reduction. The time to recovery was also related to total dose but was not prolonged by three or four sequential treatments. In all surviving mice, marrow recovery was evident 10–14 days after the first treatment.

Peripheral leukopenia observed in this study was characterized by both granulocytopenia (fig 3A) and lymphopenia (fig 3B). Severity and time to recovery were related to the total dose administered. Circulating granulocytes were more severely reduced than lymphocytes at their common nadir (Days 3–6). In survivors, leukopenia was reversed by Day 14 regardless of dose. Lymphocyte recovery slightly preceded granulocyte recovery.

The frequency distribution of platelet counts in normal male BDF_1 mice is skewed toward counts lower than the median (4.13×10^5 cells/mm^3).[6] Nevertheless, 90% of these mice have platelet counts $> 2.1 \times 10^5$/mm^3. In this context, thrombocytopenia (platelets $< 2 \times 10^5$/mm^3, fig 3C) was observed after one or more doses of 5-FU. Circulating platelets reached nadirs about 6 days after the first dose and recovered about 4 days later. Recovery was generally followed by thrombocytosis.

Myeloid:erythroid (M:E) ratios were affected by 5-FU administration (fig 3D). The high M:E ratio observed on Day 1 after 134 mg/kg × 2 probably indicates drug-induced mitotic blockade by this dose in proliferative precursor cells. Reversal of the M:E ratio after about 6 days indicates resumption of erythroid and myeloid proliferation; because mature myeloid forms dominate the marrow differential, myeloid precursors by comparison to proliferating erythroid precursors made the lesser contribution to the ratio.

Clinical chemistry studies revealed no significant deviation of the BUN or SGPT from normal levels regardless of treatment. The LDH exhibited a two-fold elevation between Days 10 and 14 in surviving recipients of all doses on one or more schedules. Histologic data do not provide a clear explanation for this LDH elevation.

5-FU administration produced a dose-dependent loss of body weight with a nadir on Day 3. The weight change was related to total dose but was independent of the dose schedule. The percent reduction of body weight on Day 3 after 33 (qd × 4), 66 (qd × 3), 200 (qd × 1), and 134 (qd × 2) mg/kg was 6%, 13%, 18%, and 22%, respectively. All survivors had recovered their lost weight by Day 21.

Injury to the gastrointestinal tract appeared to be the most consistent drug-dependent lesion disclosed by histologic examination. As indicated in table 1, a single dose of 5-FU produced a transient episode of mild intestinal epithelial change on Day 3. Extending 5-FU administration to two sequential doses (table 2) elicited a response in the intestinal epithelium on Day 1, and the evidence suggests that injury occurred early within the first 24 hours after treatment. After three sequential doses, toxicity was clearly dose-dependent. On Day 1 (table 3) epithelial hyperplasia and villar atrophy in the small intestine typified the relationship of frequency and severity of the lesions to the dose administered. Lesions were observed in 0, 20%, 40%, 80%, and 100% of animals receiving 0, 33, 66, 134, and 200 mg/kg of 5-FU, respectively, in three sequential daily doses. The severity of the lesions exhibited a similar graded increase (table 3). After four treatments, frequency and severity of lesions increased still more (table 4).

DISCUSSION

The clinical toxicity of 5-FU is characterized primarily by leukopenia, stomatitis, esophagopharyngitis, diarrhea, anorexia, nausea and vomiting, and, to a lesser extent, by thrombocytopenia, hemorrhage, gastrointestinal ulceration, alopecia, dermatitis, and nail changes (6). In patients who received 15 mg/kg/day (555 mg/m^2/day) iv × 5 days, leukopenia developed 8 days after the initiation of treatment and recovery was apparent 15 days later (9). Thrombocytopenia developed after 11 days and persisted for about 10 days (9). Leukocyte counts $< 3 \times 10^3$/mm^3 and platelet counts $< 1 \times 10^5$/mm^3

[6] Harrison SD, Jr, Burdeshaw JA, and Denine EP. Unpublished data.

TABLE 1.—Principal microscopic findings for male BDF$_1$ mice given a single dose of 5-FU

Organ-lesion	Dose mg/kg	Dose mg/m²	Days after treatment* 1	3	6	10	14	21
Small intestine								
Epithelial hyperplasia, hypertrophy, and macronucleosis	0	0	0/8	0/5	0/5	0/5	0/5	0/5
	200†	600	0/8	0/5	0/5	0/5	0/4	0/4
	134	402	0/8	2/5 (0.6)	0/5	0/5	0/5	0/5
	66	198	0/8	0/5	0/5	0/5	0/5	0/5
	33	99	0/8	0/5	0/5	0/5	0/5	0/5
Granulomatous, necrotic, or suppurative enteritis	0	0	0/8	0/5	0/5	0/5	0/5	0/5
	200	600	0/8	0/5	0/5	1/5 (0.2)	0/4	0/4
	134	402	0/8	0/5	0/5	0/5	0/5	0/5
	66	198	0/8	0/5	0/5	0/5	0/5	0/5
	33	99	0/8	0/5	0/5	0/5	1/5 (0.2)	0/5
Large intestine								
Epithelial hyperplasia, hypertrophy, and macronucleosis	0	0	0/5	0/5	0/5	0/4	0/3	0/5
	200	600	0/5	2/5 (0.6)	0/5	0/3	0/3	0/4
	134	402	0/7	3/5 (1.2)	0/5	0/4	0/3	0/5
	66	198	0/5	0/5	0/5	0/3	0/3	0/5
	33	99	0/5	0/5	0/5	0/3	0/2	0/5
Epithelial atypism and atrophic mucous glands	0	0	0/5	0/5	1/5 (0.2)	0/4	0/3	0/5
	200	600	0/5	1/5 (0.2)	0/5	0/3	0/3	0/4
	134	402	0/7	1/5 (0.4)	0/5	1/4 (0.3)	0/3	0/5
	66	198	0/5	0/5	0/5	0/3	0/3	0/5
	33	99	0/5	0/5	0/5	0/3	0/2	0/5
Suppurative, lymphoid, or ulcerative colitis	0	0	0/5	0/5	2/5 (0.6, 0.6)	1/4 (0.8)	1/3 (0.3)	0/5
	200	600	0/5	0/5	0/5	1/3 (0.7)	0/3	0/4
	134	402	0/7	0/5	0/5	1/4 (0.5)	0/3	0/5
	66	198	0/5	0/5	0/5	0/3	0/3	2/5 (0.6)
	33	99	0/5	0/5	1/5 (0.2)	0/3	0/2	0/5
Lymph node, mesenteric								
Lymphoid depletion	0	0	0/3	0/4	3/4 (1.5)	4/4 (2.0)	0/2	0/5
	200	600	0/3	4/4 (2.0)	3/3 (2.0)	3/3 (2.7)	0/2	0/4
	134	402	0/5	2/4 (1.0)	1/3 (0.7)	4/4 (1.8)	0/3	0/3
	66	198	0/3	0/5	1/3 (0.3)	1/3 (0.7)	1/3 (0.7)	0/4
	33	99	0/3	1/5 (0.4)	2/5 (0.8)	1/2 (1.0)	0/2	0/4

*No. of affected mice/No. of mice or organs examined; Nos. in parentheses = mean degree of severity using 0 = no lesion, 1 = slight, 2 = moderate, 3 = severe, and 4 = very severe.
†Historical single-dose LD10.

TABLE 2.—Principal microscopic findings for male BDF$_1$ mice given 2 sequential doses of 5-FU

Organ-lesion	Dose mg/kg	Dose mg/m²	Days after treatment* 1	3	6	10	14	21
Stomach, squamous								
Hyperplasia and acanthosis	0	0	0/5	0/5	0/5	0/5	0/5	0/4
	200†	600	2/3 (0.4)	0/5	0/6	0/3	0/3	0/1
	134	402	0/5	0/5	3/5 (0.6)	0/5	0/4	0/3
	66	198	0/5	0/5	1/5 (0.2)	0/5	0/5	0/5
	33	99	0/5	0/5	1/5 (0.2)	0/5	0/5	0/5
Hyperkeratosis	0	0	0/5	0/5	0/5	0/5	0/5	0/4
	200	600	3/5 (0.6)	0/5	0/6	0/3	0/3	0/1
	134	402	0/5	0/5	2/5	0/5	0/4	0/3
	66	198	0/5	0/5	1/5 (0.2)	0/5	0/5	0/5
	33	99	0/5	0/5	1/5 (0.2)	0/5	0/5	0/5

TABLE 2.—Principal microscopic findings for male BDF, mice given 2 sequential doses of 5-FU—Continued

Organ-lesion	Dose mg/kg	Dose mg/m²	Days after treatment* 1	3	6	10	14	21
Small intestine								
Epithelial hyperplasia, hypertrophy, and macronucleosis	0	0	0/5	0/5	0/5	0/5	0/5	0/5
	200	600	4/5 (0.8)	5/5 (1.0)	4/6 (0.8)	0/3	0/3	0/1
	134	402	0/5	4/5 (0.8)	2/5 (0.4)	0/5	0/4	0/3
	66	198	0/5	0/5	0/5	0/5	0/5	0/5
	33	99	0/5	0/5	0/5	0/5	0/5	0/5
Epithelial degeneration	0	0	0/5	0/5	0/5	0/5	0/5	0/5
	200	600	0/5	0/5	0/6	0/3	0/3	0/1
	134	402	4/5 (0.8)	0/5	0/5	0/5	0/4	0/3
	66	198	4/5 (0.8)	0/5	0/5	0/5	0/5	0/5
	33	99	0/5	0/5	0/5	0/5	0/5	0/5
Atrophic glands	0	0	0/5	0/5	0/5	0/5	0/5	0/5
	200	600	0/5	5/5 (1.0)	0/6	0/3	0/3	0/1
	134	402	0/5	4/5 (0.8)	0/5	0/5	0/4	0/3
	66	198	4/5 (0.8)	0/5	0/5	0/5	0/5	0/5
	33	99	0/5	0/5	0/5	0/5	0/5	0/5
Atrophic villi	0	0	0/5	0/5	0/5	0/5	0/5	0/5
	200	600	0/5	5/5 (1.0)	2/6 (0.3)	0/3	0/3	0/1
	134	402	0/5	4/5 (0.8)	2/5 (0.4)	0/5	0/4	0/3
	66	198	0/5	0/5	0/5	0/5	0/5	0/5
	33	99	0/5	0/5	0/5	0/5	0/5	0/5
Large intestine								
Epithelial hyperplasia, hypertrophy, and macronucleosis	0	0	0/4	0/5	0/5	1/4 (0.5)	0/5	1/5 (0.2)
	200	600	2/5 (0.4)	0/5	4/6 (0.8)	0/2	0/3	0/1
	134	402	0/4	1/5 (0.2)	2/5 (0.4)	0/4	0/4	1/3 (0.3)
	66	198	1/5 (0.2)	2/5 (0.4)	0/5	1/3 (0.3)	0/5	0/5
	33	99	1/4 (0.3)	0/5	0/5	0/4	0/5	0/5
Suppurative colitis	0	0	0/4	0/5	0/5	1/4 (0.5)	0/5	1/5 (0.2)
	200	600	0/5	0/5	0/6	0/2	1/3 (0.3)	0/1
	134	402	0/4	0/5	0/5	0/4	0/4	1/3 (0.3)
	66	198	0/5	0/5	0/5	2/3 (0.7)	0/5	0/5
	33	99	1/4 (0.3)	0/5	0/5	0/4	0/5	0/5
Glandular proliferation with reduced mucus production	0	0	0/4	0/5	0/5	1/4 (0.5)	0/5	0/5
	200	600	0/5	0/5	3/6 (1.0)	0/2	0/3	0/1
	134	402	0/4	1/5 (0.2)	3/5 (0.6)	0/4	0/4	0/3
	66	198	0/5	2/5 (0.4)	3/5 (0.6)	1/3 (0.3)	0/5	0/5
	33	99	0/4	0/5	0/5	0/4	0/5	0/5
Lymph node, mesenteric								
Lymphoid depletion	0	0	0/4	0/5	0/5	2/3 (1.7)	2/3 (1.3)	0/5
	200	600	2/2 (3.0)	0/3	4/6 (1.8)	0/2	1/2 (1.0)	0/1
	134	402	4/5 (2.4)	0/3	1/3 (0.3)	2/4 (1.3)	0/2	0/3
	66	198	3/3 (2.0)	0/3	0/4	1/3 (1.0)	0/5	0/4
	33	99	0/2	0/2	0/5	0/3	0/3	0/5
Spleen								
Lymphoid depletion	0	0	0/5	0/5	0/5	0/5	0/5	0/5
	200	600	2/3 (0.8)	0/5	1/6 (0.5)	1/3 (0.7)	0/3	0/1
	134	402	2/5 (1.0)	0/5	0/5	0/5	0/4	0/2
	66	198	2/5 (0.8)	0/5	1/5 (0.4)	0/5	0/5	0/5
	33	99	0/5	0/5	0/5	0/5	0/5	0/5

*No. of affected mice/No. of mice or organs examined; Nos. in parentheses = mean degree of severity using 0 = no lesion, 1 = slight, 2 = moderate, 3 = severe, and 4 = very severe.

†Historical single-dose LD10.

TABLE 3.—Principal microscopic findings for male BDF_1 mice given 3 sequential doses of 5-FU

Organ-lesion	Dose mg/kg	Dose mg/m²	Days after treatment* 1	3	6	10	14	21
Stomach								
Squamous hyperkeratosis	0	0	0/5	0/5	0/5	0/5	0/5	0/5
	200†	600	4/5 (0.8)	5/5 (1.0)	1/1 (2.0)	—	—	—
	134	402	4/4 (1.8)	3/5 (0.6)	0/1	—	3/3 (1.0)	2/3 (0.7)
	66	198	1/5 (0.2)	0/5	0/5	0/5	4/5 (0.8)	0/4
	33	99	0/5	0/4	0/5	0/5	0/5	0/5
Squamous hyperplasia and acanthosis	0	0	0/5	0/5	0/5	0/5	0/5	0/5
	200	600	4/5 (0.8)	5/5 (1.0)	1/1 (2.0)	—	—	—
	134	402	4/4 (1.8)	3/5 (0.6)	0/1	—	3/3 (1.0)	2/3 (0.7)
	66	198	1/5 (0.2)	0/5	0/5	0/5	4/5 (0.8)	0/4
	33	99	0/5	0/4	0/5	0/5	0/5	0/5
Small intestine								
Epithelial hyperplasia, hypertrophy, and macronucleosis	0	0	0/5	0/5	0/5	0/5	0/5	0/5
	200	600	5/5 (2.2)	5/5 (1.6)	1/1 (3.0)	—	—	—
	134	402	4/5 (2.0)	4/5 (2.0)	0/1	—	0/3	0/3
	66	198	2/5 (0.8)	5/5 (1.0)	0/5	0/5	0/5	0/4
	33	99	0/5	0/5	0/5	0/5	0/5	0/5
Vacuolar (hydropic?) degeneration of villar epithelium	0	0	0/5	0/5	0/5	0/5	0/5	0/5
	200	600	0/5	1/5 (0.4)	0/1	—	—	—
	134	402	0/5	1/5 (0.6)	0/1	—	0/3	0/3
	66	198	0/5	0/5	0/5	0/5	0/5	0/4
	33	99	0/5	0/5	0/5	0/5	0/5	0/5
Villar atrophy	0	0	0/5	0/5	0/5	0/5	0/5	0/5
	200	600	5/5 (2.2)	4/5 (2.4)	1/1 (3.0)	—	—	—
	134	402	4/5 (2.0)	4/5 (2.4)	0/1	—	0/3	0/3
	66	198	2/5 (0.8)	0/5	0/5	0/5	0/5	0/4
	33	99	1/5 (0.4)	0/5	0/5	0/5	0/5	0/5
Atrophic or cystic glands	0	0	0/5	0/5	0/5	0/5	0/5	0/5
	200	600	4/5 (1.8)	3/5 (1.8)	0/1	—	—	—
	134	402	3/5 (1.2)	2/5 (1.2)	0/1	—	0/3	0/3
	66	198	1/5 (0.2)	0/5	0/5	0/5	0/5	0/4
	33	99	1/5 (0.4)	0/5	0/5	0/5	0/5	0/5
Large intestine								
Epithelial hyperplasia, hypertrophy, and macronucleosis	0	0	0/3	0/5	0/4	0/5	0/5	0/5
	200	600	1/4 (0.8)	4/5 (1.6)	1/1 (2.0)	—	—	—
	134	402	0/3	4/5 (1.6)	—	—	1/3 (0.7)	0/3
	66	198	2/3 (1.3)	5/5 (1.8)	0/3	0/5	3/5 (1.2)	0/4
	33	99	0/4	0/5	0/3	0/5	0/5	0/5
Glandular atrophy	0	0	0/3	0/5	0/4	0/5	0/5	0/5
	200	600	3/4 (1.3)	4/5 (1.6)	0/1	—	—	—
	134	402	0/3	4/5 (1.6)	—	—	0/3	0/3
	66	198	2/3 (1.3)	5/5 (1.8)	0/3	0/5	0/5	0/4
	33	99	0/4	0/5	0/3	0/5	0/5	0/5
Suppurative colitis	0	0	0/3	0/5	0/4	0/5	0/5	0/5
	200	600	2/4 (0.8)	1/5 (0.4)	1/1 (2.0)	—	—	—
	134	402	0/3	0/5	—	—	1/3 (0.7)	0/3
	66	198	1/3 (0.7)	3/5 (0.8)	1/3 (0.3)	0/5	2/5 (1.0)	0/4
	33	99	1/4 (0.5)	0/5	0/3	0/5	0/5	0/5
Lymph node, mesenteric								
Lymphoid atrophy	0	0	0/2	0/5	0/4	0/2	0/4	0/3
	200	600	3/4 (1.8)	4/4 (3.0)	0/1	—	—	—
	134	402	2/3 (1.3)	4/5 (2.4)	—	—	0/3	0/1
	66	198	3/3 (2.0)	4/4 (1.8)	0/1	0/2	0/4	0/4
	33	99	1/2 (0.5)	0/3	0/3	0/3	0/5	0/5

TABLE 3.—Principal microscopic findings for male BDF$_1$ mice given 3 sequential doses of 5-FU—Continued

Organ-lesion	Dose mg/kg	Dose mg/m²	Days after treatment* 1	3	6	10	14	21
Spleen								
Lymphoid atrophy	0	0	0/5	0/5	0/5	0/4	0/5	0/5
	200	600	0/5	4/5 (2.2)	0/1	—	—	—
	134	402	2/5 (1.0)	1/5 (0.6)	0/1	—	0/3	0/3
	66	198	0/5	2/5 (0.8)	1/5 (0.6)	0/5	0/5	0/4
	33	99	0/5	0/5	0/5	0/5	0/5	0/5

*No. of affected mice/No. of mice or organs examined; Nos. in parentheses = mean degree of severity using 0 = no lesion, 1 = slight, 2 = moderate, 3 = severe, and 4 = very severe.
†Historical single-dose LD10.

TABLE 4.—Principal microscopic findings for male BDF$_1$ mice given 4 sequential doses of 5-FU

Organ-lesion	Dose mg/kg	Dose mg/m²	Days after treatment* 1	3	6	10	14	21
Stomach, squamous								
Hyperplasia and acanthosis	0	0	0/5	0/5	0/5	0/5	0/5	0/5
	200†	600	5/5 (1.0)	4/4 (1.0)	—	—	—	—
	134	402	5/5 (1.0)	5/5 (2.2)	—	—	—	—
	66	198	3/5 (0.6)	0/5	0/6	0/3	0/1	0/4
	33	99	0/5	0/5	0/5	0/5	0/3	0/4
Hyperkeratosis	0	0	0/5	0/5	0/5	0/5	0/5	0/5
	200	600	5/5 (1.0)	4/4 (1.0)	—	—	—	—
	134	402	5/5 (1.0)	5/5 (2.2)	—	—	—	—
	66	198	0/5	0/5	0/6	0/3	0/1	0/4
	33	99	0/5	0/5	0/5	0/5	0/3	0/4
Small intestine								
Epithelial hyperplasia, hypertrophy, and macronucleosis	0	0	0/5	0/5	0/5	0/5	0/5	0/5
	200	600	5/5 (3.0)	4/4 (3.0)	—	—	—	—
	134	402	5/5 (3.0)	5/5 (2.4)	—	—	—	—
	66	198	5/5 (1.0)	0/5	0/6	0/3	0/1	0/4
	33	99	0/5	0/5	0/5	0/5	0/3	0/4
Hydropic epithelial degeneration	0	0	0/5	0/5	0/5	0/5	0/5	0/5
	200	600	0/5	4/4 (3.0)	—	—	—	—
	134	402	2/3 (1.2)	4/5 (2.2)	—	—	—	—
	66	198	0/5	0/5	0/6	0/3	0/1	0/4
	33	99	0/5	0/5	0/5	0/5	0/3	0/4
Atrophic glands	0	0	0/5	0/5	0/5	0/5	0/5	0/5
	200	600	5/5 (3.0)	4/4 (3.0)	—	—	—	—
	134	402	5/5 (3.0)	5/5 (2.4)	—	—	—	—
	66	198	0/5	0/5	0/6	0/3	0/1	0/4
	33	99	0/5	0/5	0/5	0/5	0/3	0/4
Atrophic villi	0	0	0/5	0/5	0/5	0/5	0/5	0/5
	200	600	5/5 (3.0)	4/4 (3.0)	—	—	—	—
	134	402	5/5 (3.0)	5/5 (2.4)	—	—	—	—
	66	198	5/5 (1.0)	0/5	0/6	0/3	0/1	0/4
	33	99	0/5	0/5	0/5	0/5	0/3	0/4
Large intestine								
Epithelial hyperplasia, hypertrophy, and macronucleosis	0	0	0/3	1/5 (0.2)	0/2	0/3	0/5	0/3
	200	600	3/3 (2.0)	3/4 (1.3)	—	—	—	—
	134	402	2/2 (2.0)	5/5 (2.2)	—	—	—	—
	66	198	3/3 (2.3)	4/5 (1.2)	0/3	0/2	0/1	0/2
	33	99	2/2 (2.0)	1/5 (0.6)	0/5	0/2	0/3	1/2 (1.3)

TABLE 4.—Principal microscopic findings for male BDF_1 mice given 4 sequential doses of 5-FU—Continued

Organ-lesion	Dose mg/kg	Dose mg/m²	Days after treatment* 1	3	6	10	14	21
Atrophic and cystic glands	0	0	0/3	0/5	0/2	0/3	0/5	0/3
	200	600	3/3 (2.0)	3/4 (1.3)	—	—	—	—
	134	402	2/2 (2.0)	5/5 (2.2)	—	—	—	—
	66	198	2/3 (2.0)	4/5 (1.2)	0/3	0/2	0/1	0/2
	33	99	2/2 (2.5)	1/5 (0.6)	0/5	0/2	0/3	0/2
Subchronic, suppurative, or ulcerative colitis	0	0	0/3	1/5 (0.2)	0/2	0/3	0/5	0/3
	200	600	0/3	1/4 (0.5)	—	—	—	—
	134	402	0/2	1/5 (0.4)	—	—	—	—
	66	198	1/3 (1.0)	3/5 (0.8)	0/3	0/2	0/1	0/2
	33	99	2/2 (1.3)	1/5 (0.6)	1/5 (0.4)	0/2	0/3	1/2 (1.3)
Lymph node, mesenteric								
Lymphoid depletion	0	0	0/2	0/5	—	0/3	0/5	0/3
	200	600	2/2 (3.0)	1/1 (3.0)	—	—	—	—
	134	402	2/2 (1.5)	4/4 (2.3)	—	—	—	—
	66	198	4/4 (2.0)	2/3 (0.7)	0/2	0/2	—	2/2 (2.5)
	33	99	2/3 (1.7)	1/5 (0.4)	0/2	0/2	0/2	0/2
Spleen								
Lymphoid depletion	0	0	0/5	0/5	0/5	0/5	0/5	0/5
	200	600	4/4 (3.0)	4/4 (3.0)	—	—	—	—
	134	402	4/4 (2.0)	3/5 (1.0)	—	—	—	—
	66	198	4/4 (2.0)	0/5	0/6	0/3	0/1	0/4
	33	99	0/5	0/5	0/5	0/4	0/3	0/4

*No. of affected mice/No. of mice or organs examined; Nos. in parentheses = mean degree of severity using 0 = no lesion, 1 = slight, 2 = moderate, 3 = severe, and 4 = very severe.
†Historical single-dose LD10.

were not uncommon in these patients. Medullary granulocytopenia developed 8–12 days after the first dose and persisted until 7–10 days after treatment. Curreri et al (9) noted that this was an "extreme depression" of medullary granulocytes.

These observations have been confirmed and extended by other investigators (10–12). An early erythroid depletion was observed in the marrow of patients during 5-FU therapy. Elevated M:E ratios developed and reached a peak 8 days after the initiation of treatment (12). M:E ratios did not decline until "several days" after the last dose of 5-FU. Rectal biopsy of patients receiving 5-FU revealed histologic abnormalities within 7 days after treatment was begun (10). Dose levels, routes of administration, and schedules were similar in all these studies.

The salient features of the clinical toxicity of 5-FU are compared in table 5 with results of the present study. The BDF_1 mouse appears to provide a good qualitative and quantitative prediction of 5-FU toxicity, although the mouse apparently is quantitatively more sensitive than man. Greater sensitivity to therapeutic and toxic doses of anticancer drugs may be a general characteristic of mice (2). The 5-FU doses administered in this study (33, 66, 134, and 200 mg/kg/day—0.16, 0.33, 0.67, and 1.0 × single-dose LD10) correspond to about 100, 200, 400, and 600 mg/m²/day. We administered 5-FU to BDF_1 mice for 1–4 consecutive days. This protocol is comparable to that of Curreri et al (9) who administered 185–555 mg/m² × 5 days. The peripheral leukopenia and thrombocytopenia and medullary granulocytopenia that we observed in mice were strikingly similar in time course and magnitude to the hematopoietic depression observed in man. Moreover, our histologic observations of the gastrointestinal tracts of mice treated with 5-FU are in agreement with changes noted in the gastrointestinal mucosae of man (9,10).

Heidelberger et al (8) reported that 5-FU administered to mice produced a progressive loss of body weight. The mice in our study exhibited similar weight loss, but mice treated with sublethal doses recovered lost weight. These weight changes are probably related to the histologic changes reported by Heidelberger et al (8) and confirmed here, especially the "characteristic finding" of cessation of mitotic activity in the intestinal mucosa and villar atrophy. Mitotic arrest in the gastrointestinal mucosae of rodents following 5-FU treatment has been described by other investigators (18,19). Altered mitotic activity correlates with the localization and persistence of 5-FU metabolites in gastrointestinal

TABLE 5.—Comparison of clinical toxicity of 5-FU with present results from BDF_1 mice

5-FU treatment		Symptom (ref No.)	Day of onset*		Severity		Day of recovery*	
Man	Mouse		Man	Mouse	Man	Mouse	Man	Mouse
555 mg/m²/day × 5	200 mg/m²/day × 4	Leukopenia (2)	8	7	$< 3 \times 10^3$/mm³	$< 4 \times 10^3$/mm³	23	25
		Thrombocytopenia (2)	11	5–10	$< 1 \times 10^5$/mm³	$< 2 \times 10^5$/mm³	23	25
		Medullary granulocytopenia (2)	8	5	Extreme	Extreme‡	15	14
		Elevated M:E (15)	8	5	20 ± 10†	> 11	< 26	14
		Abnormal colorectal histology (4)	7	5–7	Toxic	Moderate	< 26	18

*Day of 1st dose = Day 0.
†Mean ± SD.
‡20% of control.

epithelia of mice treated with 5-FU (20). Marrow toxicity in mice is similarly related to 5-FU distribution and pharmacokinetics (20).

In several instances in this study, the response of some labile cell populations on Days 4 and 6 after the first of four doses of 5-FU was similar to that observed on Days 3 and 6 after a single dose. The data suggest that the animals do not respond to a fourth dose in the same way that they respond to the first dose of a sequence. The first dose appears to determine the time to recovery instead of the fourth dose. This observation may provide a rationale for manipulating 5-FU regimens to achieve higher total dose delivery without increasing the time required for recovery of vital normal cells. Whether this phenomenon can be explained in pharmacokinetic or cytokinetic terms must await further studies.

Goldsmith et al (2) suggested that an expanded role of the mouse in preclinical toxicity studies of anticancer drugs might be warranted. Mouse toxicity data are readily available, and the mouse "appears to be a reasonably good quantitative predictor for human toxicity" (2). Detailed consideration of mouse data might provide additional input for planning and interpreting clinical studies. A diversion of the emphasis on preclinical studies in dogs and monkeys is not indicated however. Previous work in our laboratories (1) and the data reported here support the indications for examining in greater detail the reliability of the mouse as a predictor of clinical toxicity.

REFERENCES

1. DENINE EP, HARRISON SD, JR, and PECKHAM JC. Qualitative and quantitative toxicity of sublethal doses of methyl-CCNU in BDF_1 mice. Cancer Treat Rep 61:409–417, 1977.
2. GOLDSMITH MA, SLAVIK M, and CARTER SK. Quantitative prediction of drug toxicity in humans from toxicology in small and large animals. Cancer Res 35:1354–1364, 1975.
3. FREIREICH EJ, GEHAN EA, RALL DP, ET AL. Quantitative comparison of toxicity of anticancer agents in mouse, rat, hamster, dog, monkey, and man. Cancer Chemother Rep 50:219–244, 1966.
4. SCHABEL FM, JR. Animal models as predictive systems. *In* Cancer Chemotherapy—Fundamental Concepts and Recent Advances. Chicago, Year Book Medical Publishers, 1975, pp 323–355.
5. SCHEIN PS, DAVIS RD, CARTER S, ET AL. The evaluation of anticancer drugs in dogs and monkeys for the prediction of qualitative toxicities in man. Clin Pharmacol Ther 11:31–40, 1970.
6. HEIDELBERGER C. Pyrimidine and pyrimidine nucleoside antimetabolites. *In* Cancer Medicine (Holland JF, and Frei E III, eds). Philadelphia, Lea and Febiger, 1973, pp 768–791.
7. MOERTEL CG. Clinical management of advanced gastrointestinal cancer. Cancer 36:675–682, 1975.
8. HEIDELBERGER C, GRIESBACH L, MONTAG BJ, ET AL. Studies on fluorinated pyrimidines. II. Effects on transplanted tumors. Cancer Res 18:305–317, 1958.
9. CURRERI AR, ANSFIELD FJ, MCIVER FA, ET AL. Clinical studies with 5-fluorouracil. Cancer Res 18:478–484, 1958.
10. FLOCH MH, and HELLMAN L. The effect of five-fluorouracil on rectal mucosa. Gastroenterology 48:430–437, 1965.
11. GOLD LG, HALL TC, SHNIDER BI, ET AL. A clinical study of 5-fluorouracil. Cancer Res 19:935–939, 1959.
12. STALZER RC, KIELY JM, PEASE GL, ET AL. Effect of 5-fluorouracil on human hematopoiesis. Cancer 18:1071–1078, 1965.
13. BONADONNA G, BRUSAMOLINO E, VALAGUSSA P, ET AL. Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 294:405–410, 1976.
14. The colorimetric determination in blood, plasma, or serum of urea nitrogen. Sigma Technical Bulletin No. 14 (Broida D, ed). St. Louis, Sigma Chemical Co, 1969, pp 1–9.
15. BERGER L, and BROIDA D. The quantitative colorimetric determination of lactic dehydrogenase. Sigma Technical Bulletin No. 500. St. Louis, Sigma Chemical Co, 1974, pp 1–19.
16. The quantitative colorimetric determination of glutamic-oxalacetic and glutamic-pyruvic transaminases. Sigma Technical Bulletin No. 505 (Broida D, ed). St. Louis, Sigma Chemical Co, 1974, pp 7–12.

17. Manual of Histologic Staining Methods of the Armed Forces Institute of Pathology, 3rd ed (Luna LG, ed). New York, McGraw-Hill Book Co, 1968, pp 32–39.
18. MUGGIA AL, WAGMAN E, MILLES SS, ET AL. Response of the gastrointestinal tract of the mouse to 5-fluorouracil. Am J Pathol 42:407–414, 1963.
19. WILLIAMS AW. Experimental production of altered jejunal mucosa. J Pathol Bacteriol 85:467–472, 1963.
20. LISS RH, and CHADWICK M. Correlation of 5-fluorouracil (NSC-19893) distribution in rodents with toxicity and chemotherapy in man. Cancer Chemother Rep 58:777–786, 1974.

Influence of Continuous Infusion of Cytosine Arabinoside on Sequencing With Daunorubicin in L1210 Leukemia [1,2]

Brief Reports and Preliminary Communications

Mark Edelstein,[3,4] Fred Valeriote,[3,*] and Teresa Vietti[3,5]

Omura has recently reported on a clinical trial (1) of our prediction (2) that cytosine arabinoside (ara-C) given 10–15 hours before daunorubicin (DNR) would be more effective than the two drugs given either in the opposite sequence or simultaneously. He was unable to confirm the superiority of a schedule in which ara-C preceded DNR, but he correctly pointed out that the major difference between the preclinical and clinical studies, ie, the method of administration of ara-C, might have influenced the result. Accordingly, we have examined here the effect of a continuous infusion of ara-C and a single dose of DNR on the sequence- and interval-dependent killing of L1210 leukemia cells.

MATERIAL AND METHODS

Four days after an iv injection of 2×10^6 L1210 cells, $CD2F_1$ (BALB/c × DBA/2) mice were given ara-C (1 mg/mouse) as a 12-hour iv infusion (3), DNR (0.25 mg/mouse) as a single iv injection, or a combination of the two agents given in either sequence with various time intervals between administration of the two agents. Twenty-four hours after administration of the agents, we assayed pooled femoral marrow of the various groups of treated animals for the numbers of leukemic colony forming units (LCFU), using the spleen colony assay (2). By comparing these results to the number of LCFU in the pooled marrow of control animals, we calculated the surviving fractions.

RESULTS

The results for the various schedules, including the mean fractional survival and the range of values obtained, are listed in table 1. DNR alone produces a mean surviving fraction of LCFU of approximately 1.5×10^{-2}; ara-C given as a 12-hour infusion produces a mean surviving fraction of LCFU of 1.1×10^{-3}. The mean additive level, approximately 1.6×10^{-5}, is the product of the survival for the individual agents and assumes independence of action for the two agents. Three different schedules were examined: the second agent given immediately, 12 hours, or 24 hours after the first. For the combinations in which ara-C was given first, if DNR followed immediately, the surviving fraction was 2.6×10^{-6}; this increased to about 10^{-5} for the other two intervals. While the results for the 12- and 24-hour intervals are not significantly different from the expected additive effect, for ara-C given immediately after DNR, a highly significant effect is obtained when compared to the additive level ($P < 0.01$ from a paired t test of a logarithmic transform of the observed minus the expected values). For the reverse order, the surviving fraction was 4.1×10^{-5} if ara-C immediately followed DNR; the surviving fraction increased to 1.6×10^{-4} for the 12-hour interval but then decreased slightly to 7.1×10^{-5} for the 24-hour interval.

DISCUSSION

A continuous infusion of ara-C combined with a single iv injection of DNR results in a surviving fraction approximately equal to that predicted for independent action of the agents generally irrespective of the order of, or interval between, administration. Cell survival is substantially less than additive if DNR is administered 12 hours before starting the

[1]Received Apr 14, 1977; revised Jan 16, 1978; accepted Jan 23, 1978.

[2]Supported by Public Health Service grant CA-13053 and contract N01-CM-43731 (Division of Cancer Treatment) from the National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare.

[3]Division of Radiation Oncology, Mallinckrodt Institute of Radiology (*Drs. Edelstein* and *Valeriote*) and Division of Hematology and Oncology, Mallinckrodt Department of Pediatrics (*Drs. Edelstein* and *Vietti*), Washington University School of Medicine, St. Louis, Mo.

[4]*Present address:* Department of Medicine, Duke University School of Medicine, Chapel Hill, NC.

[5]We wish to thank Dean Coulter and Kathy Atwood for their technical assistance.

Reprint requests to: Fred Valeriote, PhD, Section of Cancer Biology, Division of Radiation Oncology, Mallinckrodt Institute of Radiology, Washington University School of Medicine, 4511 Forest Park, Rm 411, St. Louis, Mo 63108.

TABLE 1.—Influence of interval and sequence of administration of ara-C infusion and single-dose DNR on L1210 LCFU survival

Treatment	Interval	Mean (range) LCFU survival*
1 mg of ara-C (12-hr infusion)	—	$1.1\ (0.6–1.6) \times 10^{-3}$
0.25 mg of DNR	—	$1.5\ (0.7–2.3) \times 10^{-2}$
"Additive"	—	$1.6\ (0.5–3.7) \times 10^{-5}$
DNR *after* ara-C	Immediately	$2.6\ (0.3–4.2) \times 10^{-6}$
	12 hrs	$1.0\ (0.72–1.4) \times 10^{-5}$
	24 hrs	$8.9\ (4.8–13) \times 10^{-6}$
DNR *before* ara-C	Immediately	$4.1\ (2.2–6.0) \times 10^{-5}$
	12 hrs	$1.6\ (0.91–2.3) \times 10^{-4}$
	24 hrs	$7.1\ (0.7–17) \times 10^{-5}$

*2–5 separate experiments.

ara-C infusion. However, for DNR given immediately after the completion of the ara-C infusion, a synergistic cytocidal effect is observed. The explanation given previously for single doses of these agents may also apply here (2). The ara-C infusion is expected not only to kill cells in the S phase of the cell cycle but also to block cells at the G_1/S phase junction—a point where DNR is expected to be most effective. This would explain the synergistic effect observed for DNR given immediately after the ara-C infusion. It is encouraging to note that the additive level in this study is the same as the surviving fraction obtained for the optimal time and sequence of administration of iv push doses of both ara-C and DNR examined in the previous study (2).

However, as in our previous study in which only one regimen of ara-C was administered (a single iv injection), we examined here only a 12-hour infusion. Because of the short cell cycle time of L1210, 12-hour infusions of ara-C administered to the mouse likely correspond to the more prolonged infusions in man. The potentially more effective scheduling of these two agents (DNR given immediately after ara-C infusion) has not yet been tested in man, although the effect of multiple, daily injections of DNR during a prolonged (5 or 7 days) infusion of ara-C is being examined. We are continuing our systematic study of the effect of multiple doses of DNR used in combination with ara-C infusions.

REFERENCES

1. OMURA GA. Sequencing of cytosine arabinoside (NSC-63878) and daunorubicin (NSC-82151) in acute myelogenous leukemia. Cancer Treat Rep 60:629–631, 1976.
2. EDELSTEIN M, VIETTI T, and VALERIOTE F. Schedule-dependent synergism for the combination of 1-β-D-arabinofuranosylcytosine and daunorubicin. Cancer Res 34:293–297, 1974.
3. EDELSTEIN M, VALERIOTE F, and VIETTI T. Cellular quantitation of the in vivo effects of 1-β-D-arabinofuranosylcytosine on leukemia L1210. J Natl Cancer Inst 58:941–947, 1977.

Phase II Study of Mitomycin C, Cyclophosphamide, and Methotrexate in Drug-Resistant Colorectal Carcinoma [1,2]

Brief Reports and Preliminary Communications

Cary A. Presant,* Gary Ratkin, and Carol Klahr [3]

The results of chemotherapy management of patients with metastatic colorectal carcinoma have been poor. The standard treatment in such patients is 5-fluorouracil (5-FU), a drug which produces objective responses in approximately 20% of patients (1). Most combination chemotherapy regimens include 5-FU in some schedule as part of initial treatment. However, the management of patients who have become resistant to therapy including 5-FU has not been widely reported, and indeed the discussion of the management of such patients is absent from most large reviews (1–4).

In an attempt to improve the management of patients resistant to 5-FU, we initiated a study of a combination of three drugs in such patients. Mitomycin C was chosen because of a reported objective response rate of 16%, cyclophosphamide was chosen because of a reported objective response rate of 27%, and methotrexate was chosen because of a reported objective response rate of 17% (1). An intermittent treatment schedule was considered important for patient convenience. We further considered it reasonable to treat patients previously resistant to melphalan (Alkeran), since cyclophosphamide can frequently produce responses in melphalan-resistant multiple myeloma (5).

MATERIALS AND METHODS

Patients were eligible for this treatment program if they had metastatic adenocarcinoma of the colon or rectum and had previously demonstrated an increase in measured tumor area by at least 50% during treatment with a regimen containing 5-FU in doses sufficient to produce mild-to-moderate myelosuppression or gastrointestinal toxic effects. Patients had not received any chemotherapy in the 30 days prior to entry into this study. All patients gave voluntary, informed consent before receiving drug therapy.

Therapy consisted of mitomycin C, 10 mg/m^2; cyclophosphamide, 500 mg/m^2; and methotrexate, 30 mg/m^2, all given iv on Day 1. Treatment was repeated on Day 28, and those patients with objective tumor response on Day 56 continued to receive treatment at 28-day intervals. If the nadir granulocyte count during the prior course was $< 500/mm^3$ or if the nadir platelet count was $< 50{,}000/mm^3$, the dose of each drug was reduced 50% for the next course of therapy. No chemotherapy was administered if the wbc count was $< 4000/mm^3$ or if the platelet count was $< 100{,}000/mm^3$.

A partial response (PR) was defined as a decrease of $> 50\%$ in the sum of the products of the perpendicular diameters of bi-dimensional tumors or of $> 30\%$ in the sum of the distances between the costal margin and liver edge measured in the right midclavicular line, midline, and left midclavicular line in patients with hepatomegaly.

The mean age of the 14 patients treated was 56.5 years. There were ten women and four men. Three had rectal carcinoma and 11 had colon carcinoma. The mean pretreatment performance status (Karnofsky performance scale) was 71.1%. Four patients had previously received radiation therapy to the pelvis. Prior chemotherapy consisted of 5-FU alone in two patients, 5-FU plus melphalan in seven patients, and a combination of vincristine, 5-FU by 5-day iv infusion, and CCNU in five patients. The major site of tumor involvement was the liver in eight patients, the lung in three patients, and soft tissue in five patients. All 14 patients were evaluable for antitumor response, and 12 had a sufficient number of blood tests performed to be evaluable for hematologic toxic effects.

RESULTS

PRs were obtained in four of the 14 patients. Two patients with liver involvement had PRs lasting

[1]Received Aug 17, 1977; revised Nov 21, 1977; accepted Jan 11, 1978.

[2]Supported in part by the Multimodality Oncology Project of The Jewish Hospital of St. Louis, and Public Health Service grants RR-00036 (Division of Research Resources) and CA-13053 (National Cancer Institute) from the National Institutes of Health, Department of Health, Education, and Welfare.

[3]Division of Hematology-Oncology, The Jewish Hospital of St. Louis, Washington University School of Medicine, Mo.

*_Reprint requests to:_ Cary A. Presant, MD, Division of Hematology-Oncology, The Jewish Hospital of St. Louis, 216 S Kingshighway, St. Louis, Mo 63110.

only 1 and 2 months, respectively. One patient with pulmonary metastases and soft tissue involvement in the pelvis had a PR lasting 6 months which was associated with the disappearance of sciatic pain due to tumor involvement of the lumbosacral plexus. A patient with soft tissue metastases in the pelvis had a PR lasting 2 months. An additional patient with lung metastases remained stable for 4 months. Five patients showed progression of tumor during the first 2 months of therapy, and four died during the first 2 months of therapy. No patient had a $> 10\%$ increase in performance status.

The overall response rate (four PRs in 14 patients treated) was a satisfactory 28.6%. However, the very short duration of the PRs indicated that the quality of antitumor response was poor in all but one patient. If one accepts a minimum criterion of useful PR as a duration of ≥ 3 months, only one of 14 patients had a useful PR, for a response rate of 7%. The mean duration of survival was 4.3 months, with a median of 4.5 months and a range of 2 weeks to 9 months. Five patients remain alive, two at 5 months after treatment and one each at 6, 7, and 9 months after initiation of treatment.

The dose-limiting toxic effect was myelosuppression, usually granulocytopenia. The mean nadir granulocyte count was 2500/mm^3 (range, 300–6900/mm^3). The nadir granulocyte count was < 750/mm^3 in four patients, between 750 and 1500/mm^3 in three patients, and > 1500/mm^3 in five patients. The mean nadir platelet count was 122,000/mm^3 (range, 27,000–278,000/mm^3). Two patients had a nadir platelet count $< 50{,}000$/mm^3, five between 50,000 and 100,000/mm^3, and six $> 100{,}000$/mm^3. In all instances, nadir blood cell counts were achieved 2 weeks after treatment. In nine of 13 patients, hematologic recovery had occurred by 4 weeks. In four patients, recovery was delayed until 5 weeks after the prior course of treatment. Cumulative myelosuppression (lower granulocyte or platelet count nadirs in subsequent courses compared to the first course of therapy) was observed in five of the 11 patients.

No patient experienced hepatotoxic reactions from the treatment regimen. One patient had a rise in serum urea nitrogen from 20 to 40 mg/100 ml. All patients experienced nausea and vomiting lasting from 4 to 24 hours. This was usually poorly controlled by antiemetics. The only evidence of stomatitis was diffuse soreness of the mouth, and no patient developed diffuse ulcerations.

DISCUSSION

Despite previously reported response rates of 16% for mitomycin C, 27% for cyclophosphamide, and 17% for methotrexate and no prior exposure to any of these drugs in our patients, the PR rate which was observed was disappointingly low. Although four of 14 patients had PRs, only one of those patients had a PR lasting for > 2 months. The median survival in our patients was 4.3 months, which was relatively short compared to the marked degree of toxicity (myelosuppression) produced by the regimen. No patient had an increase in performance status $> 10\%$, suggesting that subjective responses were quite consistent with the observed low objective response rate. Although only one useful response was obtained in 14 patients, the total response rate of 29% may be a clue that this combination might produce more frequent and better responses in previously untreated patients. It is also possible that previously untreated patients might tolerate higher doses of these drugs. Furthermore, 12 of the 14 patients had previously received alkylating agents (melphalan or CCNU) which might have decreased the effectiveness of the cyclophosphamide. Therefore, a trial of this regimen in previously untreated patients might be warranted.

We conclude that the combination of mitomycin C, cyclophosphamide, and methotrexate produces unsatisfactory results in the management of patients with carcinoma of the colon or rectum resistant to regimens including 5-FU. We cannot, however, predict the efficacy of this regimen in previously untreated patients.

REFERENCES

1. CARTER SK, and FRIEDMAN M. Integration of chemotherapy into combined modality treatment of solid tumors. II. Large bowel carcinoma. Cancer Treat Rev 1:111–129, 1974.
2. MOERTEL CG. Alimentary tract cancer: large bowel. *In* Cancer Medicine (Holland JF, and Frei E III, eds). Philadelphia, Lea and Febiger, 1974.
3. WASSERMAN TH, COMIS RL, GOLDSMITH M, ET AL. Tabular analysis of the clinical chemotherapy of solid tumors. Cancer Chemother Rep Part 3, vol 6(2):399–419, 1975.
4. WOOLLEY PV III, MACDONALD JS, and SCHEIN PS. Chemotherapy of colorectal carcinoma. Semin Oncol 3:415–420, 1976.
5. BERGSAGEL DE, COWAN DH, and HASSELBACK R. Plasma cell myeloma: response of melphalan resistant patients to high dose intermittent cyclophosphamide. Can Med Assoc J 107:851–855, 1972.

Recurrent Bladder Papillomata Treated With Bacillus Calmette-Guérin: A Preliminary Report (Phase I Trial) [1,2]

Brief Reports and Preliminary Communications

Y. Douville,[3] G. Pelouze,[3] R. Roy,[3] R. Charrois,[3] A. Kibrité,[3] M. Martin,[3] L. Dionne,*[3] L. Coulonval,[4] and J. Robinson†[3]

SUMMARY

Six patients with recurrent bladder papillomata were treated both by abdominal scarification with bacillus Calmette-Guérin (BCG) and by intravesical BCG, without resection. Four patients responded favorably (two showing major systemic complications), and the other two, who failed to respond, underwent further surgery.

[Cancer Treat Rep 62:551–552, 1978]

Bladder papillomata, though histologically benign, recur frequently after transurethral coagulation, and, eventually, may become malignant (1). Complementary radiotherapy or chemotherapy (2) has not, unfortunately, greatly reduced this recurrence rate.

Since bladder tumors are known to be antigenic, an immunotherapeutic approach using bacillus Calmette-Guérin (BCG) has been proposed in the hope of prolonging remissions and lessening the chances of malignant transformation (3). In animals, the relative safety of this treatment together with the positive immunologic systemic reaction it causes have been documented (4). BCG as an adjuvant to resection of bladder papillomata has already been reported in man (3). This preliminary study describes the results of BCG without surgery.

MATERIALS AND METHODS

Six patients who had had at least two recurrences of their bladder papillomata in < 2 years after resection gave informed consent for this experiment. Only one of the recurrences was biopsied, and the number and nature of the tumors were estimated (all being classed as T1 [5]). The patients then underwent abdominal scarification with 5 mg of BCG weekly × 6 weeks, followed by intravesical installation of 120 mg of BCG in 50 ml of physiologic saline retained for 2 hours. A control cystoscopy was done 4–6 weeks after treatment.

The reactions to treatment seen in our patients were classified as minor or major local and systemic symptoms. All patients who responded to BCG had dysuria, hematuria, and a flu-like syndrome. Two of our responders had hypersensitivity arthritis. Patients with major systemic complications were treated with antituberculous therapy.

RESULTS

The results are summarized in table 1. The two patients with major systemic complications completely recovered with antituberculous drugs.

DISCUSSION

All four patients who responded to BCG treatment showed local bladder irritation and evidence of minor or major systemic toxic reactions, whereas, in the two nonresponders, both of these toxic manifestations were absent. It is interesting to note that response to this form of immunotherapy could be dramatic even when there was a large total tumor present (*see* patient 5, table 1). It is possible that those patients who did not respond were or remained PPD negative, and the importance of the patients' immunologic status both before and after treatment is currently being investigated.

The major systemic reactions were easily controlled with antituberculous drugs, but the patients still required hospitalization. We are consequently trying different dose and administration schedules

[1]Received Aug 30, 1977; revised Jan 3, 1978; accepted Jan 24, 1978.

[2]BCG containing 10–30 × 10^6 organisms/mg was obtained from

[3]General Surgery Service, L'Hôtel-Dieu de Québec, Canada.

[4]Urology Service, L'Hôtel-Dieu de Québec, Canada.

†*Deceased.*

**Reprint requests to:* Dr. Louis Dionne, L'Hôtel-Dieu de Québec, 11 Côte du Palais, Québec, G1R 2J6, Canada.

TABLE 1.—BCG treatment for recurrent bladder papillomata

Patient No.	Sex	Age	No. of recurrent tumors	No. of tumors after treatment	Local complications	Systemic complications	Subsequent management
1	F	33	13	11*	None	None	Surgical resection
2	M	42	5	0	Minor	Major	Antituberculous drugs; total recovery
3	M	65	4	4	None	None	Surgical resection
4	M	65	10	0	Minor	Major	Antituberculous drugs; total recovery
5	M	57	20	0	Minor	Minor	None
6	F	55	2	0	Minor	Minor	None

*Not significant.

in an attempt to reduce the number and severity of adverse reactions to BCG.

CONCLUSION

BCG therapy for recurrent bladder papillomata is partially effective but carries a certain level of toxicity. Nevertheless, the fact that tumors regressed after BCG therapy without any resection being performed suggests that this treatment may have value in reducing future recurrence rates and malignant transformation. Further studies on these points are currently under way.

REFERENCES

1. MARSHALL VF, HOLDEN J, and MA KT. Survival of patients with bladder carcinoma treated by simple segmental resection. Cancer 9:568–571, 1956.
2. BRACKEN RB, JOHNSON DE, RODRIGUEZ L, ET AL. Treatment of multiple superficial tumors of bladder with intravesical bleomycin. Urology 9:161–163, 1977.
3. MORALES A, EIDINGER D, and BRUCE AW. Intracavitary bacillus Calmette Guérin in the treatment of superficial bladder tumors. J Urol 116:180–183, 1976.
4. SCHELLHAMMER PF, KAPLAN MH, PINSKY CM, ET AL. Study of local and systemic effects of intravesical BCG. Urology 6:562–567, 1975.
5. WALLACE DM, CHISHOLM GD, and HENDRY WF. T.N.M. classification for urological tumours (U.I.C.C.)—1974. Br J Urol 47:1–12, 1975.

Phase II Study of Baker's Antifol in Advanced Colorectal Cancer [1,2]

Brief Reports and Preliminary Communications

Fernando Padilla,[3,*] Juan Correa,[4] Thomas Buroker,[4] and Vainutis K. Vaitkevicius [4]

One postulated mechanism of drug resistance in tumors is a decrease in cell membrane permeability for those agents that enter cells via an active process (1). Baker's antifol (BAF), a nonclassic folic acid inhibitor, has evoked interest because of its ability to penetrate cells passively (1–3). BAF has been shown to produce cures in rats with Walker 256 ascites tumors whereas ineffectiveness has been noted in L1210 leukemia. Since the compound accumulates to levels 50 times greater in Walker 256 cells compared to L1210 cells, it is believed that this transport process accounts for the difference in drug responsiveness (1,3,4).

A phase I study conducted at the M. D. Anderson Hospital and Tumor Institute, Houston, Tex, utilized doses of 10–250 mg/m^2 × 5 days. Predominant toxicities included myelosuppression, dermatitis, and mucositis. Antitumor activity was demonstrated in colorectal carcinomas; however, patients with severely impaired liver function experienced life-threatening toxicities (5). A phase II study by Rodriguez et al (6) at a dose of 250 mg/m^2 × 3 days produced four partial remissions in 25 patients with colon cancer.

In an attempt to find new second-line therapies in disseminated colorectal cancer, the Southwest Oncology Group (SWOG) embarked on a phase II study in previously treated patients.

MATERIALS AND METHODS

Thirty patients with biopsy-proven colorectal cancer were entered in the study. Past chemotherapy had consisted of either 5-fluorouracil alone or in combination with mitomycin C or methyl-CCNU. No patient had received methotrexate. All patients had been off their previous chemotherapy for 3 weeks and had definite progressive disease at the time BAF was begun. Progression was defined as an increase in the size of measurable lesions by ≥ 50% or the development of new metastatic sites after having received two courses of therapy which had produced drug toxicity. Fifteen men and 15 women, with an age range of 31–72 years, were treated. Nineteen patients had a SWOG performance status[5] of 0–1, while 11 had a status of 2–3. All patients prior to treatment had a wbc count of > 4000/mm^3, a platelet count of > 100,000/mm^3, a bilirubin level of < 1.2 mg/100 ml, and a creatinine level of < 1.5 mg/100 ml.

Pretreatment liver scan, chest roentgenogram, and enzymatic liver profile were also obtained. Patients had a life expectancy of ≥ 8 weeks and signed a consent form in accordance with the respective institutional policy.

BAF (supplied by the Division of Cancer Treatment, National Cancer Institute, Bethesda, Md) was administered at a dose of 250 mg/m^2 as a 1-hour iv infusion for 3 consecutive days. Courses were repeated at 3-week intervals, providing recovery from toxicity had occurred. Doses were altered in 50-mg/m^2 increments depending upon the severity of myelosuppression, mucositis, or dermatitis. Wbc and platelet counts were checked weekly while tumor measurements and creatinine were evaluated every 3 weeks. To be evaluable for toxicity and response, a patient must have survived 3 and 6 weeks, respectively.

A complete remission was defined as the complete disappearance of all clinically recognizable tumor. Partial remission was defined as a reduction of ≥ 50% of the sum of the products of the longest perpendicular diameters of all measurable lesions. A positive liver scan was required for patients whose liver was to be followed clinically as the measurable site. A remission in these patients was defined as a decrease of ≥ 30% of the sum of the measurements below the xiphoid process and both costal margins at the midclavicular lines. Tumor

[1] Received Sept 9, 1977; revised Jan 16, 1978; accepted Jan 23, 1978.

[2] This study was conducted by the Gastrointestinal Committee of the Southwest Oncology Group.

[3] Little Rock Hospital Division, Veterans' Administration, Ark.

[4] Department of Oncology, Wayne State University School of Medicine, Detroit, Mich.

Reprint requests to: Fernando Padilla, MD, Little Rock VA Hospital, 300 E Roosevelt Rd, Little Rock, Ark 72206.

[5] SWOG performance : 0 (fully active) to 4 (totally disabled).

TABLE 1.—Myelosuppression for 1st-course BAF (250 mg/m² × 3 days)

Grade	No. of patients (total = 30 patients) with—	
	Leukopenia*	Thrombocytopenia†
1	2	0
2	2	0
3	3	0
4	0	1
5	1	0
Totals	8(27%)	1(3%)

*Grade 1 = 3900–3000/mm³; grade 2 = 2900–2000/mm³; grade 3 = 1900–1000/mm³; grade 4 = < 1000/mm³; grade 5 = fatal.

†Grade 1 = 99,000–75,000/mm³; grade 2 = 74,000–50,000/mm³; grade 3 = 49,000–25,000/mm³; grade 4 = < 25,000/mm³.

reduction was required to last for a minimum of 3 weeks to be accepted as a response.

RESULTS

A total of 106 courses of BAF were administered to 30 patients. Twenty-three patients received a second course. Sixteen of the 30 patients received a third course of therapy, ten received a fourth course, and eight received five or more courses.

RESPONSE

Twenty-nine of 30 patients were evaluable for response. One patient died from tumor progression within 2 weeks of beginning therapy. Partial remissions were noted in three patients (10%). The durations of response in the responders were 15, 24, and 37 weeks respectively. In two patients the response occurred with the first course of therapy, while in the other patient it was noted after the third course.

TOXICITY

The median wbc and platelet counts for the first course were 5000/mm³ and 220,000/mm³ respectively. For all courses the eighth day was the median for the wbc and platelet nadirs. The incidence of leukopenia and thrombocytopenia in the first course is shown in table 1. No cumulative myelosuppression was demonstrated by ridit analyses through four courses of therapy ($P = 0.97$).

Dermatitis was noted in eight of 106 courses (8%). The lesions were maculopapular in all patients except one who experienced exfoliative dermatitis. The rash had a predilection for the trunk and intertriginous areas. In five patients the eruption was pruritic. There was no correlation between dermatitis and myelosuppression. The occurrence of dermatitis was not predictable in an individual patient. Mucositis was noted in three courses.

DISCUSSION

This phase II study demonstrated minimal activity of BAF, with tolerable toxicity, in previously treated patients with advanced colon cancer. The response rate is not much different from that occurring with the classic folic acid antagonist methotrexate (7). Since there exists no effective second-line therapy for large bowel cancer, we believe further trials of BAF in combination with other agents are warranted. One possible difficulty in combining this drug with other agents is its unpredictability with regard to toxicities. In addition, the eligibility of colon cancer patients may be limited since abnormal liver function is frequently encountered.

REFERENCES

1. BAKER BR. Active-site directed irreversible inhibitors of dihydrofolate reductase. Ann NY Acad Sci 186:214–226, 1971.
2. SKEEL R, CASHMORE A, and BERTINO J. Pre-clinical trials of a new triazine antifolate (NSC-139105). Proc Am Assoc Cancer Res 14:52, 1973.
3. SKEEL RT, SAWICKI WL, CASHMORE AR, ET AL. The basis for the disparate sensitivity of L1210 leukemia and Walker 256 carcinoma to a new triazine folate antagonist. Cancer Res 33:2972–2976, 1973.
4. CASHMORE AR, SKEEL RT, MAKULU DR, ET AL. Pharmacology of a new triazine antifolate in mice, rats, dogs, and monkeys. Cancer Res 35:17–22, 1975.
5. RODRIGUEZ V, GOTTLIEB J, BURGESS MA, ET AL. Phase I studies with Baker's antifol (BAF) NSC 139105. Cancer 38:690–694, 1976.
6. RODRIGUEZ V, RICHMAN SP, BENJAMIN RS, ET AL. Phase 2 study with Baker's antifol in solid tumors. Cancer Res 37:980–983, 1977.
7. MOERTEL CG. Clinical management of advanced gastrointestinal cancer. Cancer (Suppl) 36:675–682, 1975.

Treatment of Advanced Ovarian Cancer With *cis*-Dichlorodiammineplatinum(II): Poor-Risk Patients With Intensive Prior Therapy [1,2]

Brief Reports and Preliminary Communications

Howard W. Bruckner,* Carmel J. Cohen, Robert C. Wallach, Bernard Kabakow, Gunter Deppe, Ezra M. Greenspan, Saul B. Gusberg, and James F. Holland [3,4]

SUMMARY

Nineteen patients with advanced ovarian adenocarcinoma were treated with *cis*-dichlorodiammineplatinum(II) (DDP), 50 mg/m² as an iv bolus once every 3 weeks. Prior treatment had exhausted other chemotherapeutic options or damaged the bone marrow sufficiently to contra-indicate treatment with standard drugs. All patients had evaluable tumors and evidence of failure of prior therapy. DDP produced objective responses, relieved symptoms due to tumor, and improved the patients' quality of survival. There were no serious hematologic complications due to therapy except anemia.

[Cancer Treat Rep 62:555–558, 1978]

cis-Dichlorodiammineplatinum(II) (DDP) sometimes produces regression of advanced ovarian adenocarcinoma which is resistant to radiotherapy and chlorambucil (1). DDP also produces regression of ovarian tumors when it is used as initial therapy (2). This report describes additional successful experience with DDP against previously treated advanced ovarian adenocarcinoma. The schedule and dosage for treatment differed from those in the earlier report (1). These patients were treated with single 50-mg/m² injections given once every 3 weeks.

The patients in the present study were a selected group with a poor prognosis compared to those described in the earlier report (1). They had failed to respond to several drugs or could not be given combination chemotherapy because of chronic leukopenia or thrombocytopenia due to prior treatment.

METHODS

Patients with advanced ovarian adenocarcinoma were treated with 50 mg/m² of DDP given as an iv bolus every 3 weeks until progression. This was a nonrandomized study. All patients had failed prior chemotherapy and were ineligible for other treatment because of prior chemotherapy with adriamycin or persistent leukopenia (wbcs $< 3500/mm^3$ for 3 weeks) or thrombocytopenia (platelets $< 100,000/mm^3$ for 3 weeks). Patients were eligible for treatment if they had given informed consent, had an expected survival of > 3 weeks with standard treatment of symptoms, and had a BUN < 25 mg/100 ml, creatinine < 2.0 mg/100 ml, wbcs $> 2000/mm^3$, and platelets $> 60,000/mm^3$.

Objective response was defined as a 50% reduction in the product of two measurable tumor diameters or complete disappearance of pleural effusion or ascites, refractory to diuretics and paracentesis or thoracocentesis, for ≥ 3 months. If a patient had both tumor and ascites, both were required to respond. No response was defined as no improvement in the patients' symptoms or performance. Failure was defined as the appearance of new effusions or tumors, or a 25% increase in the product of two measurable tumor diameters or worsening of symptoms or performance status for 2 weeks. Subjective response with no change (status quo) in the product of tumor diameters was defined

[1]Received Sept 15, 1977; revised Dec 20, 1977; accepted Jan 10, 1978.

[2]Supported in part by contract N01-CM-43703 (Division of Cancer Treatment) and Public Health Service grant CA-15936 from the National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare, and by the Chemotherapy Foundation Inc.

[3]Departments of Neoplastic Diseases, Obstetrics and Gynecology, and Medicine (Medical Oncology), Mt. Sinai and Beth Israel Hospitals, Mt. Sinai School of Medicine, New York, NY.

[4]We acknowledge the assistance of our colleagues in the care of the patients, and J. Silverman, J. Storch, L. Pola, and J. Stromer in data management and presentation.

**Reprint requests to:* Howard W. Bruckner, MD, Department of Neoplastic Diseases, Mt. Sinai School of Medicine, 5th Ave and 100th St, New York, NY 10029.

as relief of symptoms or recovery of ambulatory status; this was not considered equivalent to an objective response.

Side effects which were due to treatment were recorded; they included vomiting, weight loss, leukopenia (nadir, < 2000 cells/mm^3) and thrombocytopenia (nadir, < 50,000 cells/mm^3), anemia (requiring transfusion, usually hemoglobin < 8.5 g/100 ml), azotemia (BUN > 25 mg/100 ml or creatinine > 2.0 mg/100 ml), allergy, peripheral neuropathy, seizure, or abnormal liver function tests (three times normal). Instances of patients refusing to continue treatment and the reason were also recorded.

Iv fluids were not initially used in a prospective program to prevent nephrotoxicity. During the course of the study, however, a program evolved. Patients were given 1–2 liters of fluid to produce diuresis. Furosemide or mannitol were used only if fluid alone failed to produce diuresis of > 100 ml/hour. Parenteral fluids were given to correct prerenal azotemia before a patient was considered ineligible for treatment.

RESULTS

Six (31.5%) of 19 patients had objective responses due to treatment. Four (21%) of 19 additional patients had subjective responses with no evaluable change in the size of the tumor. Treatment appeared equally effective regardless of prior treatment, number of drugs, prior radiotherapy, or age of the patients (table 1). Three of 12 patients responded after having had one or two prior drugs and three of seven responded after three or more drugs. Three of seven patients responded after having had prior radiotherapy. Patients responding after one or two drugs had been treated with thioTEPA plus methotrexate or melphalan alone. Patients given additional prior drugs had also been treated with 5-fluorouracil and cyclophosphamide or adriamycin (table 1).

DDP produced side effects in every patient. Nevertheless, side effects which were treatment-limiting or life-threatening were few (three of 19 patients) (table 2); two patients had irreversible non-life-threatening nephrotoxic effects and one had peripheral neuropathy. In no instance did hematologic side effects prevent or delay treatment. There were seven patients with severe leukopenia (wbcs between 1000 and 2000/mm^3) and four with severe thrombocytopenia (platelets between 40,000 and 60,000/mm^3). Six patients required transfusions. All instances of leukopenia and thrombocytopenia were reversible and none produced infection or bleeding.

TABLE 1.—Results of treatment of ovarian cancer with DDP, 50 mg/m^2 every 3 wks

Prior therapy	No. of patients: Objective response	Status quo	Failure
No. of drugs			
1–2	3	3	6
3–4	2	1	2
> 4	1	0	1
Radiotherapy*			
+	3	1	3
–	3	3	6
	Survival (mos)		
	4, 6, 6, 9, 9+, 22	3, 6, 6, 12	1, 1, 1, 1, 2, 4, 4, 7, 7

* + = prior radiotherapy; – = no prior radiotherapy.

All four instances of nephrotoxicity evidenced by elevation in BUN and creatinine levels occurred in patients with dehydration or ascites. Two acute episodes, with BUN levels of 40 and 100 mg/100 ml, were reversible with iv fluids, furosemide, and mannitol. Treatment with fluids was started within 4 days of treatment with DDP. In contrast, abnormal BUN (40 and 50 mg/100 ml) and creatinine (3 and 4 mg/100 ml) levels discovered at the time of a return visit (2 weeks later) were only partially corrected with iv fluids and diuretics in the other two patients.

Nausea and vomiting was seen in almost every patient; only three patients had serious difficulty accepting this toxic effect. No single treatment uniformly improved the acceptance of nausea and

TABLE 2.—Side effects of treatment with 50 mg/m^2 of DDP in 19 patients with ovarian cancer*

Side effect	No. of patients: Severe	Treatment stopped
Anemia	6	
Leukopenia	7	
Thrombocytopenia	4	
Renal toxicity	2†	2
Neuropathy	1	1
Allergy	0	
Nausea and vomiting	3	
Others	2‡	

*Poor-risk patients treated with DDP after failure of prior chemotherapy for advanced ovarian adenocarcinoma.

†One patient had reversible azotemia (BUN < 40 mg/100 ml); this is the same patient who had neuropathy and discontinuation of treatment.

‡Ileus (1 patient); syncope (1 patient).

vomiting; however, iv fluids, narcotics, sleeping medications, or overnight hospitalization all improved acceptance for individual patients.

One patient developed neuropathy with symptoms of painful discomfort in the legs with a "stocking" distribution and a mild defect in proprioception. This occurred after five courses of treatment; followup was insufficient to determine if it was reversible. One patient developed syncope several hours after treatment. This was not observed by any witness, and a seizure cannot be ruled out; there was no residual neurologic defect. One patient developed ileus without mechanical bowel obstruction. The patient recovered with 3 days of conservative treatment. Both incidents are listed as side effects because similar, otherwise unexplained signs and symptoms have occurred in other patients treated with DDP in combination with other drugs (2).

DISCUSSION

This report confirms and extends earlier experience with DDP for the treatment of advanced ovarian adenocarcinoma (1). The drug sometimes produced useful responses after other therapy failed. Side effects were rarely clinically serious. A single 50-mg/m² treatment once every 3 weeks was safe in the presence of chronic leukopenia or thrombocytopenia. Nevertheless, the precaution of adequate supportive care facilities is advisable. DDP can sometimes produce pancytopenia, especially with more frequent or larger doses (3). Several patients responded after having failed more extensive prior chemotherapy than described in the cited report (1).

Our treatment of choice for initial chemotherapy for ovarian cancer is combination chemotherapy. DDP was given alone in these patients only because of its minor effect on the bone marrow. The patients in this series could not be treated with DDP in combination with other cytotoxic drugs because of low wbc or platelet counts or prior treatment with several drugs, including adriamycin.

As initial treatment in a controlled trial, DDP produced seven responses in 17 patients. It was most effective as part of combination chemotherapy with adriamycin, producing 12 responses in 18 patients (4). There has been no controlled trial demonstrating the superiority of combination chemotherapy for patients after failure of prior chemotherapy. Patients having failed prior chemotherapy have been treated with DDP plus adriamycin or DDP plus adriamycin plus cyclophosphamide by our group with better response rates (2,5). Patients failing initial therapy with DDP alone or in combination have sometimes responded to larger or more frequent bolus treatment with DDP (Bruckner HW, Wallach RC, et al, unpublished data).

The elevation of BUN and creatinine levels soon after treatment with DDP is sometimes reversible if discovered and treated early with iv fluids. The possible reversibility of early nephrotoxicity with additional fluids deserves additional testing. It is considered a safe, potentially useful procedure. The potential importance of early diagnosis to permit effective reversal of nephrotoxicity may be a new observation. This hypothesis led to prophylactic treatment with iv fluids. It is usually possible to achieve a prophylactic diuresis with fluids alone. Furosemide and, only if this fails, mannitol are used if iv fluids alone fail to produce a prophylactic diuresis of 100 ml/hour. Both furosemide and mannitol are used in cases of early posttreatment elevation in BUN and creatinine levels.

We recommend in-patient overnight treatment to provide iv fluids and to produce an effective diuresis. Patients with ascites, in particular, appear to be at an increased risk of nephrotoxicity and sometimes their iv fluids increase ascites rather than improve urine output. Adequate documentation of diuresis is essential.

These observations favoring a program of hydration were anecdotal but entirely consistent with other reports (6,7). To date, no patient treated with iv fluids has had nephrotoxic reactions provided she had diuresis at the time of treatment. The relevance of this approach which does not use furosemide or mannitol (unless fluids alone fail to produce a diuresis) to the high-dose (100–120 mg/m² of DDP) bolus treatment schedules had not been tested.

The experience reported herein supports the efficacy of DDP as a useful new drug for combination chemotherapy for advanced ovarian carcinoma. DDP is not cross-resistant with other drugs. It can be used in a full 50-mg/m² dose, which has proven effective for combination therapy.

DDP improved the quality of survival and possibly increased survival of some patients. The longest duration of survival was in patients with an objective response to treatment with DDP. The absence of treatment-limiting hematologic toxic effects provides evidence that more intensive treatment with DDP can be tested for some poor-risk patients.

REFERENCES

1. WILTSHAW E, and KRONER T. Phase II study of *cis*-dichlorodiammineplatinum(II) (NSC-119875) in advanced adenocarcinoma of the ovary. Cancer Treat Rep 60:55–60, 1976.
2. BRUCKNER HW, COHEN CJ, DEPPE G, ET AL. Chemotherapy of gynecological tumors with platinum II. J Clin Hematol Oncol 7:619–632, 1977.

3. CORDER MP, MAGUIRE LC, WITTE DL, ET AL. Weekly outpatient *cis*-platinum (II) diamminedichloride (CPDD) and diuresis with dose limiting myelosuppression. Proc Am Assoc Cancer Res and ASCO 18:344, 1977.
4. BRUCKNER HW, COHEN CJ, GUSBERG SB, ET AL. Chemotherapy of ovarian cancer with adriamycin (ADM) and *cis*-platinum (DDP). Proc Am Assoc Cancer Res and ASCO 17:287, 1976.
5. BRUCKNER HW, COHEN CJ, KABAKOW B, ET AL. Combination chemotherapy of ovarian carcinoma with platinum: improved therapeutic index. Proc Am Assoc Cancer Res and ASCO 18:339, 1977.
6. STARK JJ, HOWELL SB, and CARMODY J. Prevention of *cis*-platinum nephrotoxicity. Clin Res 25:412A, 1977.
7. HAYES DM, CVITKOVIC E, GOLBEY RB, ET AL. High dose *cis*-platinum diammine dichloride. Amelioration of renal toxicity by mannitol diuresis. Cancer 39:1372–1381, 1977.

cis-Dichlorodiammineplatinum(II) as Third-Line Chemotherapy in Advanced Ovarian Adenocarcinoma [1,2]

Brief Reports and Preliminary Communications

M. Steven Piver,* Joseph J. Barlow, Shashikant B. Lele, and Donald J. Higby [3]

Our most efficacious first-line chemotherapy for women with advanced (FIGO stages III and IV) ovarian adenocarcinoma has been the three-drug combination of actinomycin D, 5-fluorouracil (5-FU), and cyclophosphamide (ACFUCY). In a randomized prospective trial comparing ACFUCY (54 patients) to melphalan (54 patients), 53.1% of the ACFUCY patients and 34.7% of the melphalan patients responded (1). For women whose disease progressed with first-line chemotherapy, our best second-line chemotherapy is high-dose methotrexate (450–1000 mg/m^2) and cyclophosphamide. In a randomized prospective trial comparing high-dose methotrexate to high-dose methotrexate plus cyclophosphamide, we achieved a 43% response rate in those patients receiving the combination therapy as compared to only 13% for those receiving high-dose methotrexate alone (2). In a subsequent trial of 47 patients receiving high-dose methotrexate and cyclophosphamide with or without vincristine, 30% achieved a complete or partial response to this second-line therapy.[4] *cis*-Dichlorodiammineplatinum(II) (*cis*-platinum) has also been effective as second-line chemotherapy in patients with alkylating agent-resistant ovarian adenocarcinoma. Of 34 patients receiving *cis*-platinum as second-line therapy, 26.5% responded for a median duration of 6 months (3).

Because of this demonstrated activity in ovarian adenocarcinoma, a prospective trial was initiated using high-dose *cis*-platinum in all patients whose disease progressed with second-line chemotherapy. This is a report of 20 consecutive patients treated with high-dose *cis*-platinum as third-line therapy for advanced ovarian adenocarcinoma.

[1]Received Oct 3, 1977; revised Jan 17, 1978; accepted Jan 23, 1978.

[2]Supported in part by Public Health Service grant CA-05834 from the National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare.

[3]Department of Gynecologic Oncology, Roswell Park Memorial Institute, Buffalo, NY.

[4]Barlow JJ, and Piver MS. Manuscript in preparation.

**Reprint requests to:* M. Steven Piver, MD, Department of Gynecologic Oncology, Roswell Park Memorial Institute, 666 Elm St, Buffalo, NY 14263.

MATERIALS AND METHODS

Of the 20 patients treated, 13 had previously had disease progression with single-drug alkylating agent chemotherapy. Seven patients had progressed with combination chemotherapy which contained an alkylating agent, either melphalan or cyclophosphamide.

Patients were then entered into the above second-line chemotherapy studies, 13 receiving methotrexate and cyclophosphamide and seven receiving methotrexate, vincristine, and cyclophosphamide. All patients had disease progression with this combination and were entered into the *cis*-platinum study.

Seventeen patients received *cis*-platinum at a dose of 100 mg/m^2, one patient received 75 mg/m^2, and two patients received 50 mg/m^2 every 3 weeks. Patients with a normal creatinine clearance received 100 mg/m^2. The dose of *cis*-platinum was decreased to 75 or 50 mg/m^2 if the creatinine clearance was below normal. Because of a moderate decrease in creatinine clearance, two patients initially receiving 100 mg/m^2 subsequently received 75 mg/m^2 of *cis*-platinum.

Eleven patients received one course, three received two courses, four received three courses, one received six courses, and one received seven courses of *cis*-platinum. In an attempt to lessen toxicity, 40 mg of Lasix was given 1 hour before administration of *cis*-platinum. In addition, 2000 ml of one third normal saline in 5% dextrose in water with 18 g/liter of mannitol was given over a 6-hour period. The *cis*-platinum was infused over a 30-minute period. An additional 2000 ml of one third normal saline in 5% dextrose was given over a 16-hour period.

RESULTS

Toxicity

Nausea and vomiting.—Seven patients had mild nausea and vomiting, eight had moderate, and five had severe, the latter defined as almost constant

nausea and vomiting for the 24-hour period after the *cis*-platinum infusion.

Renal toxic effects.—Ten of the 20 patients had repeat creatinine clearances. Ten women with disease progression after one course of *cis*-platinum did not have repeat creatinine clearances. Of those patients having repeat creatinine clearances, three had subsequent normal clearances, five had a decrease in clearance from normal (65 ml/hour) to abnormal, and two with initially abnormal creatinine clearances inexplicably had improvement in their clearance in spite of receiving subsequent courses of *cis*-platinum. One patient developed severe renal impairment (creatinine clearance of 15 ml/hour) after one course and could not be re-treated.

Hematologic toxic effects.—There were no life-threatening hematologic toxic effects. Only two patients had severe thrombocytopenia (< 50,000 cells/mm^3) and no patients had life-threatening leukopenia (< 1000 cells/mm^3).

Hearing loss.—Four patients had significant hearing loss. Of these patients, two had severe high-frequency hearing loss and could not be re-treated with *cis*-platinum.

RESPONSE

One patient had a complete response (complete regression of all clinical tumor). There were no partial responders (50% decrease in size of measurable tumor). Four patients had no change in their tumor and 15 had progression of their ovarian malignancy. The one patient who responded to *cis*-platinum had a malignant pleural effusion and massive intra-abdominal metastases, the latter proven by biopsy; she received six courses of *cis*-platinum and had complete disappearance of her pulmonary and abdominal lesions.

DISCUSSION

cis-Platinum was used as third-line chemotherapy in 20 consecutive patients with stage III and IV ovarian adenocarcinoma, all of whom had progressed with first- and second-line chemotherapy. Significant toxic effects consisted of severe hearing loss in two patients and renal failure in one patient. These are the minimal toxicity figures, since many patients received only one or two courses and had their therapy discontinued because of disease progression. There was only one response (5%).

This minimal response rate and significant toxicity do not warrant continued trial of *cis*-platinum alone administered in this dose schedule as third-line chemotherapy in women with advanced ovarian adenocarcinoma.

Whether tumor responses and toxicity are schedule-dependent is still in question. Studies have suggested that effect is a direct function of duration of exposure to *cis*-platinum (4). Despite the relatively high doses used in this study, the duration of exposure may have been suboptimal. It has been demonstrated that prolonged infusion of the drug is associated with lower peak doses but more prolonged elevations in serum levels (5). Recent unpublished data indicate that infusions in animals result in much higher tissue levels than injections of the same doses.[5] In a phase II study at this institution utilizing frequent 6-hour infusions, the overall response rate in a variety of resistant solid tumors was approximately 30% (6). The dramatic response seen in one of our patients confirms that *cis*-platinum is capable of inducing tumor regression in ovarian carcinoma. Whether alterations in dose and mode of administration would improve the response rate in third-line patients remains to be ascertained. Our subsequent trials will evaluate the use of *cis*-platinum in conjunction with adriamycin and cyclophosphamide as third-line chemotherapy.

REFERENCES

1. BARLOW JJ, and PIVER MS. Single agent vs. combination chemotherapy in the treatment of ovarian cancer. Obstet Gynecol 49:609–611, 1977.
2. BARLOW JJ, and PIVER MS. Methotrexate (NSC-740) with citrovorum factor (NSC-3590) rescue, alone and in combination with cyclophosphamide (NSC-26271), in ovarian cancer. Cancer Treat Rep 60:527–533, 1976.
3. WILTSHAW E, and KRONER T. Phase II study of *cis*-dichlorodiammineplatinum(II) (NSC-119875) in advanced adenocarcinoma of the ovary. Cancer Treat Rep 60:55–60, 1976.
4. GALE GR, MORRIS CR, ATKINS LM, ET AL. Binding of an antitumor platinum compound to cells as influenced by physical factors and pharmacologically active agents. Cancer Res 33:813–818, 1973.
5. HIGBY DJ, BUCHHOLTZ L, CHARY K, ET AL. Kinetics of *cis*-platinum (DDP) with intensive diuresis. Proc Am Assoc Cancer Res and ASCO 18:110, 1977.
6. CHARY KK, HIGBY DJ, HENDERSON ES, ET AL. Phase I study of high-dose *cis*-dichlorodiammineplatinum(II) with forced diuresis. Cancer Treat Rep 61:367–370, 1977.

[5]Higby DJ. Personal communication.

Ataxia and Athetosis as Side Effects of Chemotherapy With Vincristine in Non-Hodgkin's Lymphoma [1]

Brief Reports and Preliminary Communications

Ugo Carpentieri* and Lillian H. Lockhart [2]

Vincristine, an alkaloid proved to be useful in the treatment of leukemia, lymphoma, and a variety of solid tumors (1), has many side effects, the major one being the involvement of the nervous system (2–5). This is a report on a case of vincristine-induced ataxia and athetosis; to our knowledge, these have not previously been described as toxic effects of this drug.

CASE REPORT

A 7-year-old white boy was admitted for a diagnostic workup of a mediastinal mass and two enlarged cervical lymph nodes. His personal history was negative for other diseases and for ingestion of drugs and toxic substances. Upon admission, his weight was 21 kg and his general condition was good; a physical examination showed an enlarged mass and lymph nodes. A diagnosis of non-Hodgkin's lymphoma was made by biopsy, and treatment with vincristine (2 mg/m^2) and prednisone (60 mg/m^2) was planned. Twenty-four hours after the first injection of vincristine, depression and agitation, uncoordinated gait, inability to handle objects, and slow writhing movements of the upper limbs abruptly appeared. No pain was present. A neurologic examination showed normal, deep tendon reflexes and muscle strength and no involvement of sensory and cranial nerves. The vital signs were normal, as were micturition and defecation. The rest of the physical examination was unremarkable. Blood, urine, and stool samples revealed no abnormality. A toxic screen was negative. The cerebrospinal fluid showed neither biochemical alteration nor abnormal cells at cytocentrifugation. The viral titers were negative. No treatment was given and the patient was observed. On the second day, his temperature rose to 101°F and paralytic ileus appeared, followed on the third day by signs of inappropriate secretion of antidiuretic hormone (Na^+: 128 mEq/liter; K^+: 3.9 mEq/liter; Cl^-: 92 mEq/liter; CO_2: 20 mEq/liter; serum osmolality: 260 mOsm/liter; and urine osmolality: 1010 mOsm/liter). A hemogram at this time showed 1800 leukocytes/mm^3 (41% neutrophils, 42% lymphocytes, and 8% monocytes) with normal reticulocyte and platelet counts. Restriction of fluids was prescribed but no medication was given. On the same day, fever, paralytic ileus, ataxia, and athetosis improved, and these signs disappeared the following day. On the fifth day, the general condition returned to normal, as did the serum electrolyte level and the hemogram. The possibility of vincristine toxicity was considered and the drug was discontinued. The symptoms and signs never recurred.

After 1 year, the patient is in good general condition without neurologic deficit. He is receiving a chemotherapeutic regimen described elsewhere (6,7), with the exception of vincristine.

DISCUSSION

The exhibition of vincristine toxicity in the form of ataxia and athetosis suggests involvement of the cerebellum and basal ganglia; to our knowledge, this has never been reported before. The unusual signs and the absence of peripheral neuropathy were misleading, as were the increased temperature and the isolated leukopenia, which occasionally occur with the use of vincristine (4,5). Cerebral dysfunction (depression and agitation) (4), although scarcely important because of its aspecificity, was present from the first day and was suggestive of a generalized infection or toxic process, which, however, could not be demonstrated. Suspicion of infectious and/or leukemic involvement of the central nervous system was discarded because of the normal pertinent laboratory values and followup studies. Multifocal leukoencephalopathy was ruled out because of the short time between injection of the drug and appearance of neurologic signs and, in retrospect, by their complete regression in 4 days without sequelae. The effect from other drugs was not considered because vincristine and prednisone

[1]Received Oct 18, 1977; revised Dec 23, 1977; accepted Jan 10, 1978.

[2]Department of Pediatrics, Division of Hematology/Oncology, University of Texas Medical Branch, Galveston.

Reprint requests to: Ugo Carpentieri, MD, University of Texas Medical Branch, Department of Pediatrics, Galveston, Tex 77550.

were the only treatments given, as indicated by the physical history and negative toxic screen. The possibility of vincristine toxicity as the cause of the motor disturbances was suggested when two well-established effects of this agent were observed: paralytic ileus and inappropriate secretion of antidiuretic hormone. The course of events in our patient suggests that a reversible disturbance in function of the cerebellum and basal ganglia had occurred as a result of treatment with vincristine (4) or the combination of vincristine and prednisone. The brief duration of symptoms and the lack of prior treatment make an immune mechanism unlikely. The acute and severe character of the response, however, does suggest an idiosyncratic hypersensitivity.

While a single experience of this kind does not, of course, firmly establish ataxia and athetosis as toxic effects of vincristine, we believe that the temporal relationship of the symptoms to the therapy in our case is highly suggestive. If our interpretation is correct, these effects of vincristine, though rare, are in keeping with the multiform nature of vincristine's more customary neurotoxicity.

REFERENCES

1. HOLLAND JF, SCHARLAU C, GAILANI S, ET AL. Vincristine treatment for advanced cancer. Cancer Res 33:1258–1264, 1973.
2. WEISS HD, WALKER MD, and WIERNIK PH. Neurotoxicity of commonly used antineoplastic agents. N Engl J Med 291:75–81, 127–133, 1974.
3. ROSENTHAL S, and KAUFMAN S. Vincristine neurotoxicity. Ann Intern Med 80:733–737, 1974.
4. KAUFMAN IA, KUNG FH, KOENIG HM, ET AL. Overdosage with vincristine. J Pediatr 89:671–676, 1976.
5. CALABRESI P, and PARKS RE. Chemotherapy of neoplastic diseases. *In* The Pharmacological Basis of Therapeutics (Goodman LS, and Gilman A, eds). New York, MacMillan Publishing Co, 1975, p 1287.
6. WOLLNER N, LIEBERMAN PH, EXELBY P, ET AL. Non-Hodgkin's lymphoma in children: results of treatment with SLA_2L_2. Br J Cancer (suppl II) 31:337–342, 1975.
7. WOLLNER N, BURCHENAL JH, LIEBERMAN PH, ET AL. Non-Hodgkin's lymphoma in children: a comparative study of two modalities of therapy. Cancer 37:123–134, 1976.

Phase II Trial of 5-Fluorouracil, Adriamycin, and Mitomycin C in Advanced Colorectal Cancer [1]

Brief Reports and Preliminary Communications

Daniel G. Haller,* Paul V. Woolley, John S. Macdonald, Lee F. Smith, Jr, and Philip S. Schein [2]

SUMMARY

Thirty-five patients with advanced measurable colorectal cancer were treated with a combination of 5-fluorouracil (5-FU), adriamycin, and mitomycin C (FAM). Objective regression of tumor was observed in six patients (17%); seven patients (20%) demonstrated stabilization of disease. The FAM regimen was generally well tolerated with toxic effects limited to bone marrow depression and mild-to-moderate nausea and vomiting. FAM combination chemotherapy did not significantly improve survival in responding patients, nor was it more effective than 5-FU alone in achieving objective regression of disease.

[Cancer Treat Rep 62:563–565, 1978]

Progress in the treatment of advanced colorectal cancer has been minimal in spite of 20 years' experience with numerous single chemotherapy agents and, more recently, the utilization of combination chemotherapy. Studies employing 5-fluorouracil (5-FU) have demonstrated objective regression in 20% of patients with measurable disease (1). Response rates > 35% have been reported with the combination of 5-FU, methyl-CCNU, and vincristine (2–4), although there is little evidence that either this or any other regimen has significantly improved the survival of patients with advanced colorectal cancer.

We have previously reported that combination chemotherapy with 5-FU, adriamycin, and mitomycin C (FAM) has produced objective responses in 55% of patients with gastric cancer (5) and in 36% of patients with adenocarcinoma of the lung (6). Adriamycin and mitomycin C in colorectal cancer have been reported to have single-agent response rates of 9% and 16%, respectively (7). In this paper, we report the results of a phase II trial of FAM chemotherapy in 35 patients with advanced measurable colorectal cancer.

MATERIALS AND METHODS

Thirty-five consecutive patients with histologically proven colorectal adenocarcinoma were entered into this study. The clinical data for these patients are as follows. The patients' ages ranged from 39 to 76 years (median, 58 years). All patients were ambulatory with a median Eastern Cooperative Oncology Group performance status of 1 (range, 0–3). Fifteen of these patients had failed prior chemotherapy or radiotherapy regimens. Fourteen patients had been treated with 5-FU, methyl-CCNU, and vincristine and one had been treated with weekly 5-FU. Two additional patients had received radiation therapy to lesions in the abdomen. All patients had disease that was readily measured by physical examination, roentgenograms, or radionucleide scans prior to beginning therapy. Measurements of lesions found on liver scans were taken in anteroposterior and lateral views and were correlated in most instances with ultrasonography and/or computerized tomography. These sites included: liver (31 patients), abdomen (five patients), lung (four patients), and pelvis (two patients). A partial response (PR) was defined as a decrease of > 50% in the products of the two largest perpendicular diameters of measurable lesions; if hepatomegaly was chosen as the followable lesion, a response was defined as a decrease of > 30% in the sum of the measurements below the xiphoid process and both costal margins at the midclavicular line. Patients who demonstrated no evidence of progressive disease or who had a < 50% decrease in the size of lesions were classified as having stable disease. Patients in whom more than one site of disease was present were required to show response in all sites.

[1]Received Nov 14, 1977; revised Jan 16, 1978; accepted Jan 24, 1978.

[2]Division of Medical Oncology, Vincent T. Lombardi Cancer Research Center, Georgetown University School of Medicine, Washington, DC.

Reprint requests to: Daniel G. Haller, MD, Division of Medical Oncology, Vincent T. Lombardi Cancer Research Center, Georgetown University School of Medicine, 3800 Reservoir Rd, NW, Washington, DC 20007.

TABLE 1.—FAM chemotherapy schedule

Drug (dose schedule)	Administered on Day(s)—							
	1	8	15	22	29	36	43	50
5-FU (600 mg/m² iv)	×	×			×	×		
Adriamycin (30 mg/m² iv)	×				×			
Mitomycin C (10 mg/m² iv)	×							

TABLE 2.—Dose reductions based on blood cell counts performed prior to treatment

% drug dose	Wbcs/mm³	Platelets/mm³
100	> 3500	> 100,000
50	2500–3499	75,000–99,999
0	< 2500	< 75,000

FAM chemotherapy was administered as outlined in table 1. 5-FU was given iv at a dose of 600 mg/m² on Days 1, 8, 29, and 36 of a 56-day cycle; adriamycin was given iv at a dose of 30 mg/m² on Days 1 and 29; and mitomycin C was given iv at a dose of 10 mg/m² on Day 1. Dose modifications were made according to wbc and platelet counts performed before each treatment (table 2). Tests of liver and renal function were obtained in each patient prior to beginning therapy, and significant elevation in serum bilirubin (> 1.5 mg/100 ml) was considered a criterion for exclusion from this study. Patients who had received prior chemotherapy or radiation therapy were required to have blood cell counts which were acceptable for 100% of the calculated dose. In addition, they must also have passed the expected time of the acute hematologic toxicity of their previous therapy; in most instances, this ranged from 2 to 6 weeks.

RESULTS

PRs were observed in six of 35 patients (17%) treated with FAM chemotherapy, including two patients who had failed prior chemotherapy. Regression of hepatic lesions was documented in two patients by the use of radioisotope scans, computerized tomography, and ultrasonography. Two patients demonstrated responses in abdominal masses, whereas pulmonary nodules and malignant hepatomegaly were the followable lesions in two remaining patients. The median duration of response was 4.5+ months (range, 3+–12+ months). The median survival for the responding group was 5.5+ months (range, 3+–13+ months), and four patients are alive in continued response.

Seven patients (20%) demonstrated stabilization of disease with a duration of 7 months (range, 3–9 months). The median survival for this group was 9+ months (range, 4+–14 months) with four patients alive. The median survival for the 22 nonresponding patients is 6.5+ months but will not be > 8 months. Performance status did not significantly affect the likelihood of response since 16 of 22 nonresponding patients had performance scores of 0 or 1.

Mild-to-moderate nausea and vomiting, usually occurring on Days 1 and 29, was the most common clinical toxic effect. In no patient was this toxic effect responsible for dose reductions.

Hematologic toxic effects, usually occurring during the fifth week of each cycle, were similar to those reported in patients receiving FAM for gastric (5) or pulmonary (6) adenocarcinomas. The median wbc count nadir for all patients in this study was 3.1×10^3/mm³ (range, $1.4–5.6 \times 10^3$/mm³). The median nadir of the platelet count was 103×10^3/mm³ (range, $26–328 \times 10^3$/mm³). The differences in wbc and platelet count nadirs among the three response groups were not statistically significant. Dosage reductions were required in 13 patients (25% reduction in ten patients and 50% reduction in three patients) and, of these, nine had received prior therapy. Equal proportions of patients with responsive, stable, and nonresponsive disease had reductions in drug dose.

There were no episodes of sepsis or bleeding attributable to FAM chemotherapy, nor were there any drug-related deaths. After receiving 70 mg/m² of adriamycin, one patient with a history of heart disease developed significant congestive heart failure. The responding tumor rapidly progressed when chemotherapy was discontinued.

DISCUSSION

Lymphomas, leukemias, and breast cancer are among those tumors which have shown significant improvement in response rates and survivals with combination chemotherapy when compared to the results with single-agent therapy. Combination therapy, chiefly utilizing 5-FU with other active agents, is capable of improving objective response rates in colorectal cancer. However, no study has shown improved survival for patients treated with these regimens. Initial studies of FAM chemotherapy in patients with gastric carcinoma have shown a response rate of 55% (5), which is greater than would be expected from the activity of each of the component drugs used alone. The present study using FAM in colorectal cancer demonstrates that only 17% of patients achieved objective regression of disease; this percentage is consistent with the

activity expected from the use of 5-FU or mitomycin C alone. Regardless of response, no survival benefit was demonstrated.

The results of this phase II study suggest that the combined use of 5-FU, adriamycin, and mitomycin C, in spite of proven activity in other adenocarcinomas (5,6), is not indicated in patients with colorectal cancer. Early detection of colorectal cancer and identification of more active single agents for advanced disease remain the most promising areas of study.

REFERENCES

1. MOERTEL CG. Clinical management of advanced gastrointestinal cancer. Cancer (suppl) 36:675–682, 1975.
2. MOERTEL CG, SCHUTT AJ, HAHN RG, ET AL. Brief communication: Therapy of advanced colorectal cancer with a combination of 5-fluorouracil, methyl-1,3-*cis*(2-chlorethyl)-1-nitrosourea, and vincristine. J Natl Cancer Inst 54:69–71, 1975.
3. FALKSON G, and FALKSON HC. Fluorouracil, methyl-CCNU and vincristine in cancer of the colon. Cancer 38:1468–1470, 1976.
4. MACDONALD JS, KISNER DF, and SMYTHE T. 5-Fluorouracil (5-FU), methyl-CCNU, and vincristine in the treatment of advanced colorectal cancer: phase II study utilizing weekly 5-FU. Cancer Treat Rep 60:1597–1600, 1976.
5. WOOLLEY P, MACDONALD J, ROSENOFF S, ET AL. Treatment of advanced gastric cancer with combination chemotherapy: 5-fluorouracil (F) or ftorafur (FUR) plus adriamycin (A) and mitomycin C (M) (FAM and FAM II). Proc Am Assoc Cancer Res and ASCO 18:304, 1977.
6. MACDONALD J, BUTLER T, SMITH F, ET AL. 5-Fluorouracil (5-FU), adriamycin (ADR), and mitomycin-C (MMC), FAM, for advanced adenocarcinoma of the lung. Proc Am Assoc Cancer Res and ASCO 18:306, 1977.
7. CARTER SK, and FRIEDMAN M. Integration of chemotherapy into combined modality treatment of solid tumors. II. Large bowel carcinoma. Cancer Treat Rev 1:111–129, 1974.

LETTERS

Hexamethylmelamine, Bleomycin, and CCNU Chemotherapy for Patients With Squamous Cell Carcinoma, Large Cell Carcinoma, and Adenocarcinoma of the Lung Unresponsive to Cyclophosphamide, Adriamycin, Methotrexate, and Procarbazine [1]

Several cytotoxic drug combinations are available for the treatment of squamous cell carcinoma, large cell carcinoma, and adenocarcinoma of the lung (non-oat cell bronchogenic carcinoma [NOBC]), stages III_{M0} and III_{M1}, including our own institutional protocol of CAMP (cyclophosphamide, adriamycin, methotrexate, and procarbazine) (1–3). Approximately one half of all patients treated with any regimen will fail to respond. Almost all of those patients who initially responded, in our experience, relapsed after about 12 months (3). However, the median survival time of responders in other centers (1,2) was 9 and 6 months respectively.

Recent reports of the use of hexamethylmelamine, bleomycin, and CCNU (HBC) in NOBC (4–7) have led us to treat patients with stages III_{M0} and III_{M1} who failed on CAMP with a combination using these three agents. Patients with biopsy-proven NOBC, stage III_{M0} or III_{M1}, who were entered in the CAMP protocol and who showed progression after a minimum of three cycles (3 months) were eligible for HBC combination chemotherapy.

The HBC chemotherapy regimen is as follows: (*a*) hexamethylmelamine—300 mg/m^2 orally in four divided doses per day × 21 days (Days 1–21), repeated every 6 weeks; (*b*) bleomycin—15 units iv, once weekly × 3 weeks, repeated every 6 weeks for a total of 20 doses (300 units); and (*c*) CCNU—100 mg/m^2 orally on Day 1, repeated every 6 weeks.

Hexamethylmelamine was discontinued when the wbc count was $< 4000/mm^3$. The initiation of hexamethylmelamine and CCNU was withheld until the wbc count reached $5000/mm^3$ and the platelet count reached $\geq 150{,}000/mm^3$.

Pulmonary function studies, arterial blood gases, and a chest roentgenogram were done on each patient prior to HBC therapy. The studies were to be repeated monthly while the patients were receiving bleomycin. Cbc counts were done weekly to determine the nadir for the wbc and platelet counts.

The parameters to evaluate responses were chest roentgenograms and gallium, bone, liver, EMI, and brain scans. Reduction of the sum products of all measurable lesions (greatest tumor diameter and its perpendicular) was used to determine responses. A complete remission (CR) was defined as no evidence of disease on chest roentgenogram or scan for ≥ 2 months. A partial response (PR) was defined as $\geq 50\%$ reduction for ≥ 2 months in the sum products of all measurable lesions. Stable disease (SD) was defined as no progression or $< 50\%$ reduction for ≥ 2 months. No response (NR) was defined as progressive disease.

Survival data were calculated from the first day of chemotherapy. Evaluable patients for response to HBC required a minimum of a 1-month survival.

Thirteen patients with NOBC who were treated with the CAMP regimen and eventually progressed were entered in the HBC second-line combination therapy program (table 1). There were nine men and four women with a median age of 54 years (range, 35–68). Six of the patients had adenocarcinoma, four had squamous cell carcinoma, two had large cell carcinoma, and one had bronchoalveolar carcinoma. All patients were stage III; five were without (M_0) and eight were with (M_1) distant metastases. The initial responses to CAMP were as follows: CR (two patients), PR (three patients), SD (three patients), and NR (five patients). After a median of eight cycles of CAMP (range, 3–23 cycles), the treatment was switched to HBC. After a median of one cycle of HBC (range, 1–2 cycles), all of these patients were evaluated as NR. The sites of disease progression before and during treatment with HBC in these patients were: bone (six patients), lung (four patients), brain (one patient), liver (one patient), and axillary mass (one patient). The patient with the brain metastasis was treated with whole-brain radiation prior to HBC. Survival after the start of HBC ranged from 4.5 to 19 weeks with a median of 5 weeks. The median survival time for

[1]Supported in part by Public Health Service grant CA-14599 from the National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare.

TABLE 1.—Characteristics, pathology, and response of 13 patients treated with HBC for progressive NOBC unresponsive to CAMP

Patient No.	Patient age/sex	Histopathology	Pathologic stage	No. of cycles of CAMP	Initial response to CAMP	Performance status at start of HBC*	Sites of progression prior to HBC initiation	HBC (% dose)			No. of cycles of HBC	Toxicity		Survival since start of HBC (wks)	Survival since start of CAMP (mos)
								Hexamethylmelamine	Bleomycin	CCNU		Wbc nadir ($\times 10^3$/mm^3)	Platelet nadir ($\times 10^3$/mm^3)		
1	49/M	Adenocarcinoma	III_{M1}	4	NR	4	Lung	100	100	100	1	3.2	110	4½+	5+
2	42/M	Squamous cell carcinoma	III_{M1}	12	PR	5	Bone	100	100	100	1	1.8	165	4½	12
3	68/M	Adenocarcinoma	III_{M1}	3	NR	7	Lung	100	100	100	1	2.1	220	6½+	4+
4	47/F	Squamous cell carcinoma	III_{M1}	23	CR	4	Bone	100	100	100	1	1.2	180	5	22
5	46/M	Bronchoalveolar carcinoma	III_{M1}	16	CR	6	Axillary mass	100	100	100	2†	1.4	22	14	20
6	35/M	Adenocarcinoma	III_{M1}	8	PR	6	Bone	75	100	50	2‡	2.4	211	19	13½
7	57/F	Squamous cell carcinoma	III_{M0}	3	NR	3	Lung	100	100	100	1	11.3	379	5	5½
8	58/F	Adenocarcinoma	III_{M1}	8	PR	7	Bone	50	100	50	1	2.2	44	10	12
9	43/M	Large cell carcinoma	III_{M0}	6	NR	5	Bone	100	100	100	1	14.8	233	5	8
10	54/M	Large cell carcinoma	III_{M0}	11	NR	7	Lung	100	100	100	1	7.1	11	6	11½
11	42/F	Adenocarcinoma	III_{M0}	6	SD	5	Bone	50	100	50	1	3.1	245	4½	10
12	64/M	Squamous cell carcinoma	III_{M1}	9	SD	4	Liver	100	100	100	1	6.1	20	4½	9½
13	62/M	Adenocarcinoma	III_{M0}	4	SD	6	Brain	100	100	100	1	4.6	79	10+	7½+

*Karnofsky performance scale.
†Second cycle dosage—hexamethylmelamine, 75%; bleomycin, 100%; CCNU, 75%.
‡Second cycle dosage—hexamethylmelamine, 100%; bleomycin, 100%; CCNU, 100%.

the entire group of 13 patients from the start of CAMP was 10 months (range, 4–22).

There were only minimal toxic effects from the HBC drug combination. All of the patients had mild nausea and occasional vomiting on the first and second day of the cycle. Leukopenia (wbc count $< 4000/mm^3$) was noted in eight of the 13 patients with a nadir occurring at 3–4 weeks after starting treatment. Thrombocytopenia ($< 150{,}000$ cells/mm^3) occurred in six patients with the nadir occurring at 4–5 weeks after starting treatment. No neurologic toxicity with hexamethylmelamine was noted in the present study.

The 13 patients in this study had advanced metastatic NOBC that eventually failed our first-line combination of CAMP (3). The drug combination of HBC used by us as a second-line chemotherapy in these patients failed to achieve any objective response. All patients showed progression of the disease. Although our study deals with a rather small number of patients and a short treatment duration, no additive or synergistic effect of these drugs, given concurrently, could be seen, but they may be antagonistic.

Although other reasons for the failure of this combination could include a poor performance status at the time of instituting HBC, inadequate dosages (leukopenia in only 61% and thrombocytopenia in only 46%), or even unfavorable sites of recurrence (bone, six patients), HBC at the dose and schedule employed cannot be recommended for treatment of patients with advanced NOBC who failed previous chemotherapy.

REFERENCES

1. LANZOTTI VJ, THOMAS DR, HOLOYE PY, ET AL. Bleomycin (NSC-125066) followed by cyclophosphamide (NSC-26271), vincristine (NSC-67574), methotrexate (NSC-740), and 5-fluorouracil (NSC-19893) for non-oat cell bronchogenic carcinoma. Cancer Treat Rep 60:61–68, 1976.
2. LIVINGSTON RB, FEE WH, EINHORN LH, ET AL. BACON in squamous cell lung cancer. Cancer 37:1237–1242, 1976.
3. BITRAN JD, DESSER RK, DEMEESTER TR, ET AL. Cyclophosphamide, adriamycin, methotrexate, and procarbazine (CAMP)—effective four-drug combination chemotherapy for metastatic non-oat cell bronchogenic carcinoma. Cancer Treat Rep 60:1225–1230, 1976.
4. HANSEN HH, SELAWRY OS, MUGGIA FM, ET AL. Clinical studies with 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (NSC-79037). Cancer Res 31:223–227, 1971.
5. WILSON WL, VAN RYZIN J, WEISS AJ, ET AL. A phase III study in lung carcinoma comparing hexamethylmelamine (NSC-13875) to dibromodulcitol (NSC-104800). Oncology 31:293–309, 1975.
6. WILSON WL, ANDREW NC, FRELICK RW, ET AL. Preliminary report on the use of CCNU (NSC-79037), adriamycin (NSC-123127), and hexamethylmelamine (NSC-13875) in carcinoma of the lung. Cancer Treat Rep 60:269–271, 1976.
7. WAMPLER GL, MELLETTE SJ, KUPERMINC M, ET AL. Hexamethylmelamine (NSC-13875) in the treatment of advanced cancer. Cancer Chemother Rep 56:505–514, 1972.

Uri Mintz
Jacob D. Bitran
Judith A. Cooksey
Richard K. Desser
Tom R. DeMeester
Harvey M. Golomb

Departments of Medicine and Surgery
University of Chicago Hospitals and Clinics
and Department of Medicine
Michael Reese Medical Center
University of Chicago
Chicago, Ill 60637

January 24, 1978

Raynaud's Phenomenon After Vinblastine-Bleomycin Chemotherapy

Teutsch et al (1) reported the case of a 17-year-old boy with stage III testicular carcinoma (mixed embryonal teratocarcinoma) who developed severe Raynaud's phenomenon after 360 units of bleomycin and 75 mg of vinblastine/m^2. They speculated that bleomycin was the more likely causative agent, but noted that the two drugs might have acted synergistically. We have recently observed a similar patient in whom the sequence of events suggests that vinblastine was the major cause of the Raynaud's phenomenon.

A 22-year-old man had a right inguinal orchiectomy in October 1973 for teratocarcinoma of the testis. After lymphangiography and 2100 rads of ^{60}Co teletherapy, a bilateral retroperitoneal lymphadenectomy was done; six nodes contained teratocarcinoma. Subsequently, a left pulmonary nodule was noted, and after 2 months of chemotherapy with chlorambucil, methotrexate, and actinomycin D, and 4600 rads of ^{60}Co teletherapy, a left upper lobectomy was carried out; several nodes containing teratoma were found in the resected specimen.

Bleomycin-vinblastine chemotherapy was then instituted. A total of 405 units of bleomycin (205 mg/m^2) was given im from December 1974 to March 1975. A total of 438 mg of vinblastine (221 mg/m^2) was given iv from December 1974 to February 1977. The final 15 mg of bleomycin was given on March 31, 1975. Left pleuritic pain occurred in May 1975, and in June 1975 a small, bloody left pleural effusion was noted.

In December 1976 the patient noted cold painful white fingers in cold weather. Vinblastine therapy was discontinued in February 1976. In March 1976 the patient's hands were constantly cold (more painful in cold weather), especially the distal 4 cm

of each digit. The Raynaud's phenomenon improved in the summer, but in the winter of 1977–1978 it recurred and was quite distressing. Guanethidine has given partial symptomatic relief.

In this young man, a nonsmoker with negative antinuclear antibody test and no cryoglobulins, Raynaud's phenomenon developed 22 months after bleomycin was discontinued and while he was still being treated with vinblastine. This sequence of events suggests that vinblastine was the probable etiologic factor in the genesis of the Raynaud's phenomenon in this instance. I believe that Raynaud's phenomenon should be added to the list of adverse effects of vinblastine, which also includes myelosuppression, peripheral neuropathy, headaches, body aches, alopecia, local tissue damage after extravasation, and possibly mental depression.

REFERENCE

1. TEUTSCH C, LIPTON A, and HARVEY HA. Raynaud's phenomenon as a side effect of chemotherapy with vinblastine and bleomycin for testicular carcinoma. Cancer Treat Rep 61:925–926, 1977.

Harvey Rothberg

Princeton Medical Center
Princeton, NJ 08540

March 2, 1978

Chronic Bleomycin-Associated Raynaud's Phenomenon

Teutsch et al (1) reported a case of acute-onset acral vasospastic phenomenon (Raynaud's) in a patient being actively treated with bleomycin and vinblastine for stage III mixed cell carcinoma of the testis. Other possible causes for this process were ruled out by appropriate studies, and clearing of the symptoms occurred with discontinuance of the bleomycin therapy. Possible pathogenetic mechanisms were discussed.

I wish to report a similar case in which the Raynaud's phenomenon developed *after* completion of bleomycin therapy and has assumed a recurring and persistent course in the face of apparent "cure" of this patient with disseminated carcinoma.

CASE REPORT

A 32-year-old white man had a right orchiectomy on August 12, 1975, with the histopathology showing embryonal cell carcinoma. A chest roentgenogram showed evidence of multiple and bilateral pulmonary nodules. He began to receive combination bleomycin and vinblastine therapy and demonstrated prompt clearing of the pulmonary nodules within 4 weeks. A total dose of 580 mg of bleomycin was given over a 5-month period, from August 22, 1975, to January 30, 1976. Consolidation therapy with adriamycin, cyclophosphamide, and actinomycin D has been given since then, with continuance of complete clinical remission; the patient was last seen on September 5, 1977. He has complained of typical Raynaud's phenomenon of both hands and feet related to cold exposure (especially hunting and fishing) since February of 1977; this was ameliorated by taking extra-dress (warmth) precautions in anticipating potential provocative situations. Vasospasmolytic drugs have not been required. Acral cold-water immersion has elicited the expected blanching and cyanosis of the hands and feet; all laboratory studies seeking evidence of collagen vascular disease (cryoglobulins, antinuclear antibodies, and lupus erythematosus cell preparations performed three times were negative; dermal biopsy was not performed) or recurrent carcinoma have been normal.

It seems apparent that not only may one see acute bleomycin-associated small-vessel disease with active therapy, but that late development of this condition may occur and possibly persist in a chronic fashion. However, the possibility that this represents a completely coincidental and unrelated phenomenon to chemotherapy cannot be completely ruled out.

REFERENCE

1. TEUTSCH C, LIPTON A, and HARVEY HA. Raynaud's phenomenon as a side effect of chemotherapy with vinblastine and bleomycin for testicular carcinoma. Cancer Treat Rep 61:925–926, 1977.

Allen R. Soble

Oakland Internists Associates
23077 Greenfield Rd
Suite 205
Southfield, Mich 48075

January 10, 1978

Raynaud's Phenomenon After Bleomycin Treatment

Teutsch et al (1) reported a case of Raynaud's phenomenon associated with chemotherapy using vinblastine and bleomycin for testicular carcinoma. We recently encountered a similar patient with stage II testicular carcinoma receiving adjuvant chemotherapy consisting of vinblastine at a dose of 7.5 mg/m^2 iv on Day 1 and bleomycin at a dose of 15 mg/m^2 iv on Days 1 and 5; both drugs were repeated every 21 days. Three months following the start of

therapy, the patient began to complain of intermittently cyanotic fingers. He stated that when his hands were "exposed to cold air," the tip of his left middle finger turned very pale. After the fingers warmed up, the tip turned blue.

Physical examination at that time revealed cyanosis of the distal third, fourth, and fifth digits of the hands bilaterally, with the radial and ulnar arteries on both sides being patent. Laboratory studies, consisting of serum protein electrophoresis, cryoglobulins, antinuclear factor titer, serum immunoglobulins, latex fixation, and fibrinogen, were all negative or within normal limits. Cold agglutination titer was 1:8. Chemotherapy was continued.

Five months after the start of chemotherapy, ischemic changes in the tip of the left third digit in addition to Raynaud's phenomenon were noted. Phenoxybenzamine HCl, 10 mg/day, was started and gradually increased to 10 mg four times daily. In addition, chemotherapy was discontinued. The condition of his fingers improved markedly, did not worsen with the resumption of the chemotherapy 6 weeks after its discontinuation, and, in fact, slowly continued to improve. The bleomycin was discontinued at a total dose of 391 units. The patient continues to receive vinblastine. This case appears to represent another instance of Raynaud's phenomenon associated with vinblastine and bleomycin which also improved with blocking-agent therapy.

REFERENCE

1. TEUTSCH C, LIPTON A, and HARVEY HA. Raynaud's phenomenon as a side effect of chemotherapy with vinblastine and bleomycin for testicular carcinoma. Cancer Treat Rep 61:925–926, 1977.

D. P. Chernicoff
R. M. Bukowski
J. R. Young

Department of Hematology and Medical Oncology
and Department of Peripheral Vascular Diseases
The Cleveland Clinic
9500 Euclid Ave
Cleveland, Ohio 44106

January 10, 1978

Malignant Melanoma (Stage IIIB): A Pilot Study of Adjuvant Chemo-Immunotherapy[1]

The treatment of malignant melanoma which has metastasized to the regional lymph nodes (stage IIIB, M. D. Anderson staging classification) is difficult and disappointing; the 5-year survival of patients after surgery is in the region of 20% (1). The necessity for a form of adjuvant therapy for these patients prompted us to design a pilot study of adjuvant chemotherapy and immunotherapy after surgery for stage IIIB malignant melanoma. Possibly the most successful drug to have been assessed in melanoma is DTIC which has been reported to give regression rates of around 20% (2). DTIC was used alone in combination with immunotherapy in the first protocol of our study (D/BCG group) and in the second protocol, it was combined with two other drugs, BCNU and hydroxyurea (DBH/BCG group); these latter two agents have been shown to be active in malignant melanoma (2).

Augmentation of cell-mediated immune responses to melanoma-associated antigens by nonspecific or specific immunization may be beneficial to the host, although this concept has not been supported by clear experimental data (3). Two types of immunotherapy were examined: (*a*) BCG given intradermally, and (*b*) BCG given orally.

In view of the relatively small numbers of patients with malignant melanoma seen each year in Alberta (Canada), we have been obliged to use, as controls, a historical group of patients treated by surgery alone in this institute between 1958 and 1972. We acknowledge the many difficulties of interpretation of data using historical controls but we feel this is justifiable in a pilot study.

TABLE 1.—Clinical data

Clinical feature	Treatment group		
	D/BCG	DBH/ BCG	Historical controls
No. of—			
Men	8	10	17
Women	3	9	16
Age in yrs			
Range	27–77	27–78	22–86
Median	45	47	46
No. of patients with site of primary tumor in—			
Trunk	4	4	13
Head and neck		2	10
Extremities	7	12	10
Unknown		1	
Disease-free interval from surgery in mos			
Median	14	11	8.2
Range	4–29+	3+ –31	
Survival from surgery in mos			
Median	23	17	11
Range	8–29+	6+–31+	

[1]Presented at the International Conference on the Adjuvant Therapy of Cancer, Tucson, Ariz, Mar 2–5, 1977.

PATIENTS, MATERIALS, AND METHODS

Patients with histologically confirmed stage IIIB (disease limited to the draining regional nodes) malignant melanoma were entered into the study. The extent of disease was determined by clinical examination, chest roentgenogram with whole-lung (1 cm) tomography, radioisotope scanning of the liver, bones, and brain, cbc count, and full SMA-12 panel. Table 1 shows the clinical features of the patients entered into the study.

Two adjuvant therapy protocols were assessed. In the first protocol, DTIC was administered at a dosage of 250 mg/m^2 × 5 days iv every 21 days. BCG (Connaught, 40 mg in 1 ml of diluent) was given on Days 7, 12, and 17 in at least 20 sites using a 20-needle Heaf gun in two parallel strips over the paraspinal region of the back, using 40 mg of vaccine on each day. The 21-day cycles were repeated for 12 courses of treatment (D/BCG group).

In the second protocol, patients received DTIC at a dose of 150 mg/m^2 × 5 days iv every 28 days, in combination with iv BCNU on the first day of each cycle at a dose of 150 mg/m^2, and hydroxyurea orally at a dose of 1500 mg/m^2 on Days 1–5 of each cycle. Following chemotherapy, the patients received BCG orally at a dose of 120 mg on Days 5–10 of each cycle (DBH/BCG group). The above cycle was repeated every 28 days for six cycles and thereafter every 3 months for four cycles.

Patients were followed up at regular monthly intervals and had monthly chest roentgenograms, tomograms (whole-lung, 1-cm cuts) every 3 months, and liver, brain, and bone scans every 6 months. Adjuvant therapy was stopped when evidence of disease progression appeared. Subsequent treatment was generally unsuccessful and consisted of single-agent chemotherapy. Statistical analysis was performed and the significance of survival and disease-free intervals was compared by the modified Wilcoxon test (4).

RESULTS AND DISCUSSION

Eleven patients received the first protocol (D/BCG) and 19 patients received the second protocol (DBH/BCG). The disease-free intervals from the time of surgery of the two groups of adjuvant therapy patients were compared to the disease-free interval of the historical control group of 33 patients. There was no significant difference in the disease-free intervals of either the DBH/BCG group and the historical control group ($Z = 1.93$) or the D/BCG group and the historical control group ($Z = 1.465$). If the disease-free intervals of the two adjuvant therapy groups are combined and compared to the disease-free interval of the historical control group, the results again fail to achieve statistical significance ($Z = 2.175$). The median disease-free interval was 14 months for the D/BCG group, 11 months for the DBH/BCG group, and 8 months for the historical control group.

The survival rates of patients treated by the two adjuvant protocols were compared to a historical control group treated by surgery alone. There was a significant improvement in survival rate for the DBH/BCG group at the 0.05 level ($Z = 2.249$), but this was not seen in the D/BCG group ($Z = 1.733$) where only 11 patients were treated. When the survival rates of the D/BCG groups were combined and compared to the historical control group, the improvement in survival was significant at the 0.01 level ($Z = 2.597$). The median survivals in the D/BCG and DBH/BCG groups were 23 and 17 months, respectively. The median survival of the historical control group was 10.5 months. Thus, there is an *apparent* improvement in survival of between 6 and 13 months in the two adjuvant groups over the historical group.

The toxic effects of the chemo-immunotherapy were significant. Nausea and vomiting (particularly on the first day of treatment), fatigue, and lethargy were common side effects during treatment. Bone marrow suppression was present in most patients receiving either adjuvant regimen. Two patients died while receiving treatment; both were disease-free at autopsy. One patient died of acute laryngeal spasm and the other of myocardial infarction not obviously related to the chemotherapy.

The side effects of oral BCG immunotherapy were generally mild, although one patient developed pulmonary granulomata requiring isoniazid treatment.

The combination of systemic chemotherapy and immunotherapy has not, in this pilot adjuvant study, yielded results which might encourage a full-scale controlled trial. There was no significant improvement in disease-free intervals. The apparently improved survival compared to a group of historical controls did not justify the significant toxic manifestations of the adjuvant chemo-immunotherapy, and current regimens should probably be withheld until distant metastases develop.

Survival rates of patients after a maximum of 3 years' followup are approaching the results achieved by surgery alone in the historical group. The lack of any improvement in disease-free interval but the apparent improvement in survival may be related to improvements in diagnostic techniques (eg, liver scanning which gives more accurate staging) and to the fact that most of the historical group did not

receive modern chemotherapy when distant metastases had developed.

Until more active chemotherapeutic agents are available, future approaches to the adjuvant therapy for stage IIIB malignant melanoma should probably concentrate on immunotherapeutic measures which have more acceptable toxicity.

REFERENCES

1. LUCE JK, MCBRIDE CM, and FREI E, III. Melanoma. *In* Cancer Medicine. Philadelphia, Lea & Febiger, 1973, chap 29, p 1834.
2. LUCE JK. Chemotherapy of malignant melanoma. Cancer 30:1604–1615, 1972.
3. COCHRANE AJ. The biology and treatment of malignant melanoma. Eur J Cancer 12:585–594, 1976.
4. GEEHAN EA. A generalized Wilcoxon test for comparing arbitrarily singly-censored samples. Biometrika 52:203–223, 1965.
5. SCHAPIRA D, and MCPHERSON TA. Oral BCG pneumonitis. N Engl J Med. In press.

Alexander H. G. Paterson
T. Alexander McPherson
D. J. Willans[2]

Department of Medicine
Dr. W. W. Cross Cancer Institute
Edmonton, Alberta T6G 1Z2, Canada

January 6, 1978

[2]We express our sincere gratitude to Mrs. Merline Watson and Mr. John Hanson for their help in this study, and to the surgeons in the province who referred patients for entry into the study.

Systemic Epithelioid Granulomata Following Immunotherapy With Methanol Extracted Residue of Bacillus Calmette-Guérin

In June 1975, a 44-year-old white woman underwent an excision of a lesion to the right of the spinal column at the level of the scapula. The pathologist classified the lesion as malignant melanoma, Clark's level 5. In August 1975, the patient underwent an elective right axillary lymph node dissection and two of the 28 lymph nodes that were removed were found to contain metastatic malignant melanoma. The patient then began to receive immunotherapy with the methanol extracted residue (MER) of bacillus Calmette-Guérin, receiving 200 μg intradermally in each of four sites at 3-week intervals for 2 years. In May 1976, a lesion was excised from the right shoulder which was found to represent an epithelioid granuloma. In May 1977, a second nodular lesion appeared on the right arm which was an epithelioid granuloma. Both lesions were remote from the MER injection sites. In August 1977, a chest roentgenogram revealed a 1-cm nodule in the right lower lobe. Because of a high index of suspicion that this nodule represented recurrent malignant melanoma involving the lung, the patient was hospitalized and a search for additional areas of metastatic disease was made. When no metastases were found, the patient underwent an open thoracotomy; the nodule identified on the roentgenogram was found to represent an epithelioid granuloma. Injections with MER were continued after excision of both skin lesions. The only toxic effects attributable to MER were local and consisted of induration and ulceration. At no time did fever or chills develop after an injection with MER to indicate an inadvertent iv injection.

This case report demonstrates that the intradermal injection of MER may result in the intravascular circulation of immunogenically active material which can result in granulomas at distant foci. These granulomas, if large enough, may be confused with metastases from the original tumor.

Ira S. Jaffrey

446 Rte 304
Bardonia, NY 10954

January 9, 1978

Rhabdomyolysis as a Complication of 5-Azacytidine[1,2]

The drug 5-azacytidine, a cytidine analog, is useful in the treatment of acute nonlymphocytic leukemia resistant to standard chemotherapy (1). The side effects of this drug, including gastrointestinal, hepatic, hematopoietic, and encephalopathic toxic effects, have been well documented (1). This report calls attention to another neuromuscular toxic effect of 5-azacytidine: severe muscle tenderness and weakness with rhabdomyolysis.

CASE REPORT

A 26-year-old white woman with acute myelogenous leukemia was treated with 5-azacytidine after having a partial remission from the combination of 6-thioguanine, cytosine arabinoside, and daunorubi-

[1]Supported by Public Health Service grant CA-15688 from the National Cancer Institute (NCI), National Institutes of Health, Department of Health, Education, and Welfare.

[2]5-Azacytidine was supplied by the Cancer Therapy Evaluation Program, Division of Cancer Treatment, NCI, Bethesda, Md.

cin. The 5-azacytidine was given as an iv bolus of 300 mg/m²/day in three divided doses × 5 days.

On the second day of chemotherapy, extremely painful, generalized muscle tenderness and weakness developed. Oliguria was present for 48 hours. During the second and third days of therapy, marked lethargy, confusion, and agitation appeared.

The blood creatine phosphokinase isoenzyme 3 (derived from skeletal muscle) rose from 2 units/liter on the second day of drug administration to > 3000 units/liter by the fifth day (normal, < 120 units/liter), and there was myoglobin in the urine. The blood aldolase rose to 40 units/liter (normal, 3–8 units/liter), the urine myoglobin rose to 76 mg/liter (normal, < 4.0 mg/liter), and the serum creatinine increased from 0.6 to 2.0 mg/dl over a 3-day period.

There was no prior history of rhabdomyolysis or muscle disease. Several weeks prior to 5-azacytidine chemotherapy the patient had developed β-antigen-negative hepatitis; the SGPT was 794 units/liter at the start of chemotherapy.

By 5 days after chemotherapy, the muscle tenderness markedly diminished, the blood creatine phosphokinase and urine output returned to normal, and the creatinine decreased to 1.0 mg/dl. However, the patient did not achieve remission and died 1 month later. A post-mortem examination demonstrated hemosiderosis, central necrosis of the liver, and normal muscle histology.

COMMENTS

Despite the absence of muscle necrosis at the time of post-mortem examination, this patient has compelling evidence for rhabdomyolysis using clinical criteria (2). The generalized muscle pain, which began on the second day of 5-azacytidine administration, progressed to severe discomfort (upon movement) by the fifth day and was followed by the abatement of symptoms and normalization of urine output and muscle enzymes 7 days after therapy. Similar neuromuscular symptoms have been noted by Levi and Wiernik (3). Their patients developed these symptoms during the same time course while receiving 5-azacytidine by iv bolus on a 200 mg/m²/day × 5 schedule. No mention, however, was made as to whether their patients had rhabdomyolysis with myoglobinuria.

The etiology of muscle necrosis in our patient is not clear. Most patients studied by Levi and Wiernik (3) had "impaired hepatic reserve"; similarly, our patient was recovering from hepatitis. Abnormal metabolism of the drug may therefore have predisposed the patient to rhabdomyolysis.

Hepatic coma has been reported in about 0.5% of patients receiving 5-azacytidine. Bellet and co-workers (4) reported four deaths from hepatic encephalopathy when 5-azacytidine was given to patients with pre-existing liver derangement. Their report along with our experience suggest that administration of 5-azacytidine to patients with impaired liver function requires extreme caution.

REFERENCES

1. VON HOFF DD, SLAVIK M, and MUGGIA FM. 5-Azacytidine. A new anticancer drug with effectiveness in acute myelogenous leukemia. Ann Intern Med 85:237–245, 1976.
2. ROWLAND LP, and PENN AS. Myoglobinuria. Symposium on clinical neurology. Med Clin North Am 56:1233–1256, 1972.
3. LEVI JA, and WIERNIK PH. A comparative clinical trial of 5-azacytidine and guanazole in previously treated adults with acute nonlymphocytic leukemia. Cancer 38:36–41, 1976.
4. BELLET RE, MASTRANGELO MJ, ENGSTROM PF, ET AL. Hepatotoxicity of 5-azacytidine (NSC-102816) (a clinical and pathologic study). Neoplasma 20:303–309, 1973.

H. Phillip Koeffler
Charles M. Haskell*

Department of Medicine
University of California
School of Medicine
Los Angeles, Calif 90024

January 26, 1978

*To whom reprint requests should be sent.

Gynecomastia With Nitrosourea Therapy

Our recent experience with BCNU treatment of hematologic malignancies suggests that gynecomastia may be a previously unrecognized toxic manifestation of nitrosourea therapy. Although busulfan (1) and combination chemotherapy with MOPP (mechlorethamine, vincristine, prednisone, and procarbazine) (2) have been reported to be associated with gynecomastia, we are not aware of an association of this phenomenon with nitrosourea therapy. Recently, three patients under our care developed gynecomastia while being treated with chemotherapeutic regimens which included BCNU. The following brief summaries outline the clinical course of these patients.

Patient 1.—This 63-year-old white man with nodular poorly differentiated lymphocytic lymphoma involving the retroperitoneum and abdominal lymph nodes failed to respond to three monthly cycles of cyclophosphamide and prednisone (CP). He

also received allopurinol and isoniazid. His treatment was then changed to monthly BCNU at a dose of 120 mg/m^2 and prednisone at a dose of 100 mg/m^2 on Days 1–5. After the third course of BCNU, he complained that tenderness and tingling in both breasts began 5 days after BCNU administration, persisted for several days, and then subsided gradually over the following 2 weeks. Both nipples were noted to be engorged, erect, and tender during this and subsequent episodes. Thereafter, he received maintenance therapy with BCVP: monthly BCNU (60 mg/m^2), cyclophosphamide (600 mg/m^2), and vincristine (1.2 mg/m^2) with prednisone (100 mg/m^2) given on Days 1–5. He complained of episodes of nipple tenderness after each course of therapy, and, after three monthly courses, palpable gynecomastia developed. Following the attainment of a complete remission (CR), treatment was discontinued, and the gynecomastia disappeared within 2 months. Plasma testosterone at the time gynecomastia was noted was 417 ng/100 ml (normal, 300–1000 ng/100 ml).

Patient 2.—A 31-year-old white man with recurrent Hodgkin's disease was treated with BCVPP: monthly BCNU (100 mg/m^2), cyclophosphamide (600 mg/m^2), and vinblastine (5 mg/m^2) with procarbazine (100 mg/m^2) and prednisone (60 mg/m^2) given on Days 1–10. His other medications were levothyroxine, prescribed as replacement therapy for hypothyroidism, and allopurinol. During therapy, the patient experienced daily morning nausea occasionally accompanied by vomiting. After six cycles of BCVPP the patient's disease was in CR, but he developed a 2-cm firm mobile nonfluctuant tender breast mass underlying the left nipple. The areolae were not enlarged or hyperpigmented. A biopsy of the mass revealed male breast tissue with gynecomastia. Specifically, stromal fibrosis and hyperplasia of ductal epithelium were noted. This hyperplasia was very prominent in some areas and resulted in a papillary pattern. Focal apocrine metaplasia was noted. The fibrous stroma was loose and edematous around the ducts. The serum cortisol level was 10.7 μg/100 ml (normal, 5–20 μg/100 ml) with an increase to 30.6 μg/100 ml after a 4-hour adrenocorticotropic hormone stimulation test. The serum T_4 level was 4.4 μg/100 ml (normal, 4–10 μg/100 ml) and the serum T_3 resin-sponge uptake was 27% (normal, 25%–35%). The prolactin level was 6 ng/ml (normal, 2–11 ng/ml) and the serum testosterone level was 619 ng/100 ml (normal, 300–1000 ng/100 ml).

Patient 3.—An 83-year-old white man was treated for multiple myeloma; he received monthly BCNU (75 mg/m^2) and cyclophosphamide (400 mg/m^2) with prednisone (75 mg) given on Days 1–7. Each cycle was preceded by Compazine (10 mg). He had taken digoxin and Dyazide for years for clinically stable congestive heart failure. After the eighth course of treatment, this patient noted tenderness and swelling in his left breast and was found to have a soft round 3-cm subareolar mass with a tender, raised, normally pigmented nonerythematous nipple overlying it. A biopsy showed hyperplasia of the ductal epithelium. Hyperplastic epithelium formed short papillary projections within the lumen. There was fibrosis of the stroma which was loose and edematous around the ducts and denser in the remainder of the interstitium. These findings supported the clinical diagnosis of gynecomastia. The serum testosterone level was 285 ng/100 ml, the prolactin level was 12 ng/ml, the luteinizing hormone level was 4.8 mIU/ml (normal, 0–11 mIU/ml), the thyroid-stimulating hormone level was 4 mIU/ml (normal, 0–14 mIU/ml), the T_4 level was 4.2 μg/100 ml with a T_3 resin-sponge uptake of 28%, the follicle-stimulating hormone level was 14.6 mIU/ml (normal, 4–25 mIU/ml), and the estradiol level was 22 pg/ml (normal, 12–34 pg/ml).

None of the patients had known liver disease or history of alcohol abuse, testicular atrophy, or significant weight change.

Although gynecomastia can perhaps be explained by alternative mechanisms in patients 2 and 3, the reasons for implicating BCNU in the etiology of the gynecomastia in these patients are the following: (*a*) the strong temporal association with therapy, (*b*) the high frequency (three of 26) in patients treated with BCNU in our clinic, (*c*) the lack of convincing alternate causes in patient 1, and (*d*) the fortuitous "controlled study" of patient 1, whose gynecomastia was not present when he received CP therapy but appeared when BCNU replaced cyclophosphamide and disappeared when BCNU was discontinued.

These three patients were a part of a group of 26 patients treated in our clinic during the same time interval with chemotherapeutic regimens containing BCNU. We did not observe gynecomastia in any patient treated with other chemotherapeutic regimens during the same interval.

Although gynecomastia has been observed following MOPP therapy of adolescent males (2), these patients were found to have elevated follicle-stimulating hormone and luteinizing hormone and decreased testosterone levels. Recently, a two- to fivefold increase in serum estrogen levels has been demonstrated in rats treated with melphalan, cyclophosphamide, dibromodulcitol, or hexamethylmelamine (3). The possible mechanism by which BCNU may cause gynecomastia is not apparent, but our observations suggest that it is different from MOPP-induced adolescent gynecomastia.

REFERENCES

1. GUNZ F, and BAIKIE AG. Leukemia, 3rd ed. New York, Grune and Stratton, 0000, p 337.
2. ZIEGLER JL, SHERINS RJ, and OLWENY CLM. Gynecomastia and gonadal dysfunction in adolescent boys treated with MOPP. Proc Am Assoc Cancer Res and ASCO 18:286, 1977.
3. BOGDEN AE, ESBER HT, TAYLOR DJ, ET AL. Effect of antineoplastic agents on the endocrine system. Proc Am Assoc Cancer Res and ASCO 18:106, 1977.

Anna E. Schorer
Martin M. Oken*
Gerhard J. Johnson

Hematology Section
Veterans' Administration Hospital
and Department of Medicine
University of Minnesota
Minneapolis, Minn 55417

January 31, 1978

*To whom reprint requests should be sent.

Inactivity of DL-Amygdalin Against Human Breast and Colon Tumor Xenografts in Athymic (Nude) Mice[1]

We performed experiments designed to assess the effects of DL-amygdalin (laetrile) alone or in combination with β-glucosidase on human tumor xenografts in athymic (nude) mice. These compounds were obtained from the Division of Cancer Treatment, National Cancer Institute, Bethesda, Md. The anticancer activity of DL-amygdalin is proposed to depend on the release of HCN in the presence of β-glucosidase or β-glucuronidase (1).

The tumors used in our study were (*a*) a mammary carcinoma (MX-1) diagnosed as an infiltrating duct cell carcinoma, established in nude mice in 1974 from the surgical tissue of an untreated 29-year-old woman, and (*b*) an adenocarcinoma of the colon (CX-2) which was initially established in tissue culture in 1973 using surgical tissue from a 50-year-old man with no previous therapy, and was subsequently implanted and maintained in nude mice. These tumors were obtained from Dr. B. C. Giovanella, Stehlin Foundation for Cancer Research, Houston, Tex.

Nude mice of a random-bred NIH Swiss background were supplied by the Frederick Cancer Research Center, Md. Groups of nude mice (five mice per group) were housed under filter-top cages with autoclaved food and bedding. The mice were maintained in a specially designed barrier facility.

[1]Supported by contract N01-CM-67099 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare.

In these experiments, a 3-mm^3 tumor fragment was implanted sc by trocar into the right subaxillary region of each mouse. The mice were subsequently observed twice weekly and the tumors were measured with slide calipers when they became palpable. Mice were randomized into test groups of four to six mice each and treatment was initiated when tumors were growing progressively. The length and width of the subcutaneous tumors were measured periodically and the volume in mm^3 (v) was calculated for an ellipsoid by the modified formula $v = (a^2 \times b)/2$, where a is the width in mm and b is the length in mm. This is considered a valid estimation of weight in mg assuming unit density. The variable tumor sizes of the different groups were standardized by obtaining relative tumor weight (RW) calculated by the formula $RW = W_i/W_0$, where W_i is the mean tumor weight of a group at any given time and W_0 is the mean initial tumor weight of that group when treatment was begun. For evaluation purposes, any treatment group with an $RW < 42\%$ of that of the untreated control group is considered significantly responsive to therapy (2).

The results of the first experiment are shown in figure 1. There was no effect on either of the tumors at any of the doses tested. Some mortality was seen at all doses although gross manifestation of toxicity (eg, weight loss, organ lesion, or atrophy) was absent. The apparent reduction in RW on Day 25 (Day 45 after tumor implant) of the MX-1 group treated with 1600 mg/kg of DL-amygdalin was due to the death of one mouse with a very large tumor.

In a subsequent experiment, the CX-2 colon tumor was used to determine if DL-amygdalin in combination with β-glucosidase was active against the tumor. The results of this experiment are shown in table 1. Treatment was initiated on Day 14 after tumor implantation using a qd × 9 schedule. There was no antitumor effect in animals receiving this treatment regimen when compared with the control mice given saline. As shown in the table, the combination of 200 mg of DL-amygdalin plus 5 mg of β-glucosidase was highly toxic; all four mice were dead 2 days after the first injection. Some mice in other treatment groups died later in the test period long after the injection schedule was completed.

These experiments demonstrate that DL-amygdalin has no therapeutic effect against the MX-1 mammary or CX-2 colon tumor xenografts in athymic mice whether the drug is administered as a single agent or in combination with β-glucosidase. This drug was reported to be inactive against transplantable mouse tumors (3–5) and to exhibit increased toxicity in combination with β-glucosidase (3,4).

In previous tests using established anticancer

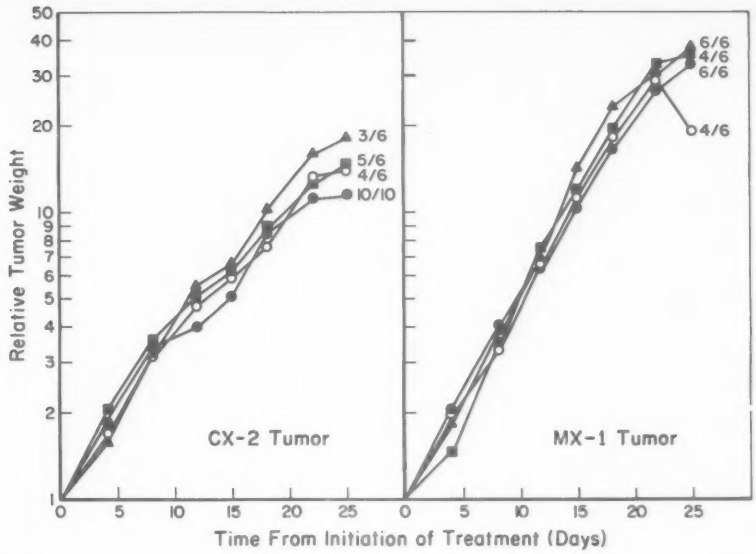


FIGURE 1.—Activity of DL-amygdalin against human CX-2 colon and MX-1 mammary xenografts in athymic (nude) mice. Treatment was started on Day 20 after tumor implantation and was given ip on a q4d × 4 schedule. ○——○ = 1600 mg/kg/injection; ▲——▲ = 800 mg/kg/injection; ■——■ = 400 mg/kg/injection; ●——● = untreated control. Nos. on curves = No. of mice surviving/total No. of mice.

TABLE 1.—Activity of DL-amygdalin and/or β-glucosidase against CX-2 human colon xenograft in female athymic (nude) mice*

Group No.	Drug	Dose (mg/kg/injection)	Initial mean tumor weight (mg)	Relative tumor size on different days after initial treatment							No. of survivors/total No. treated
				7	11	14	18	21	25	28	
1	DL-Amygdalin	800	161.1	4.0	7.1	10.6	11.0	16.1	13.5	24.3	2/4
2	DL-Amygdalin	400	153.1	3.9	6.7	10.4	10.4	13.1	14.1	21.9	3/4
3	DL-Amygdalin	200	193.3	4.2	6.9	10.2	11.9	13.7	12.2	23.0	2/4
4	DL-Amygdalin	100	202.0	3.3	5.1	7.5	8.8	9.6	11.5	17.5	3/4
5	β-Glucosidase	10	175.4	2.4	5.6	8.5	10.2	13.9	17.5	27.5	4/4
6	β-Glucosidase	5	239.8	3.1	4.8	7.3	8.6	11.0	13.2	23.9	4/4
7	DL-Amygdalin + β-glucosidase	200 5	147.2	—	—	—	—	—	—	—	0/4
8	DL-Amygdalin + β-glucosidase	100 10	192.8	3.6	5.2	8.0	8.5	10.2	12.3	22.5	2/4
9	DL-Amygdalin + β-glucosidase	100 5	250.3	3.4	4.9	7.1	8.1	9.5	13.0	22.5	4/4
10	DL-Amygdalin + β-glucosidase	50 10	149.0	4.1	7.4	11.2	14.9	15.5	19.9	32.9	4/4
11	DL-Amygdalin + β-glucosidase	50 5	144.0	3.5	6.0	8.7	10.1	13.3	17.3	31.6	4/4
12	Control	Saline	227.7	3.4	5.8	8.5	9.2	13.0	14.6	22.7	8/8

*Treatment was started on Day 14 after tumor implantation and was given ip on a qd × 9 schedule.

agents, the MX-1 tumor was eradicated completely by treatment with 67–100 mg/kg/injection of cyclophosphamide on a q4d × 4 schedule (6). Melphalan at a dose of 10 mg/kg/injection, q4d × 3, also induced complete tumor regression with no recurrence (unpublished data). The growth of the CX-2 tumor was significantly inhibited by a single treatment with 30–40 mg/kg of methyl-CCNU (7).

REFERENCES

1. STECHER PG, ed. The Merck Index, 8th ed. Rahway, NJ, Merck and Co, Inc, 1968.
2. GERAN RI, GREENBERG NH, MACDONALD MM, ET AL. Protocols for screening chemical agents and natural products against animal tumors and other biological systems, third edition. Cancer Chemother Rep Part 3, vol 3(2):1–103, 1972.
3. WODINSKY I, and SWINIARSKI JK. Antitumor activity of amygdalin MF (NSC-15780) as a single agent and with β-glucosidase (NSC-128056) on a spectrum of transplantable rodent tumors. Cancer Chemother Rep 59:939–950, 1975.
4. LASTER WR, JR, and SCHABEL FM, JR. Experimental studies of the antitumor activity of amygdalin MF (NSC-15780) alone and in combination with β-glucosidase (NSC-128056). Cancer Chemother Rep 59:951–965, 1975.
5. HILL GJ, SHINE TE, HILL HZ, ET AL. Failure of amygdalin to arrest B16 melanoma and BW5147 AKR leukemia. Cancer Res 36:2102–2107, 1976.
6. OVEJERA AA, and HOUCHENS DP. Chemotherapeutic response to cyclophosphamide (CY) of a human breast carcinoma growing in athymic (nude) mice. Proc Am Assoc Cancer Res and ASCO 18:37, 1977.
7. OVEJERA AA, HOUCHENS DP, and BARKER AD. Sensitivity of a human tumor xenograft in nude (athymic) mice to various clinically active drugs. *In* Proceedings of the 2nd International Workshop on Nude Mice (Nomura T, and Oshawa N, eds). Tokyo, Tokyo University Press, 1977.

Artemio A. Ovejera
David P. Houchens
Anna D. Barker

Battelle Memorial Institute
505 King Ave
Columbus, Ohio 43201

John M. Venditti

Division of Cancer Treatment
National Cancer Institute
Bethesda, Md 20014

February 6, 1978

Subject Index

A

A–649 (NSC–38270), phase I and preliminary phase II evaluation of, *53*:71
A–6413 (NSC–51954), preliminary clinical trial of, *50*:667
Abstracts
reports presented at the annual meeting of the American Society of Clinical Oncology, March 1969, *53*:83
reports presented at the annual meeting of the American Society of Clinical Oncology, March 1973, *57*:87
***N*-Acetyl-L-cysteine (NSC–111180)**, protection with, against isophosphamide toxicity and enhancement of therapeutic effect in early murine L1210 leukemia, *57*:299
1-Acetyl-2-picolinoylhydrazine (NSC–68626)
analogs, antitumor activity of, *58*:803
clinical pharmacologic study of, *53*:131
in children with various malignant neoplasms, *59*:341
in the treatment of advanced cancer, *53*:291
treatment of carcinoma of the lung with, *54*:243
Acronycine (NSC–403169), evaluation in the C1300 murine neuroblastoma model, *59*:975
Actinic keratosis, therapy of, with local application of vitamin A acid, *55*:59
Actinomycin D (NSC–3053)
chemical structure of, *58*:117
clinical use of, *58*:49
clinical use of, *58*:117
combination therapy including vincristine for malignant solid tumors in children, *52*:489
combined with procarbazine and vinblastine in the treatment of malignant melanoma, *59*:767
combined with vincristine and alternating with adriamycin in the treatment of advanced sarcomas, *59*:1035
combined with vincristine and cyclophosphamide with or without radiation therapy in the treatment of childhood rhabdomyosarcoma, *59*:359
cytologic studies on human melanoma cells in tissue culture, *52*:543
effect of, on several parameters of, in infection by Friend spleen focus-forming virus, *52*:557
evaluation of, in experimental systems, *58*:63
history and chemistry of, *58*:1
in the treatment of acute leukemia in children, *57*:335
in the treatment of Wilms' tumor, *58*:5
plus vincristine and cyclophosphamide for embryonal rhabdomyosarcoma, *58*:281
single-dose toxicity of, in dogs, *59*:447
some determinants of the therapeutic efficacy of, and of adriamycin and daunorubicin, *58*:55
stereochemistry of, binding to DNA, *58*:101
7-substituted analogs of, as fluorescent DNA-binding and experimental antitumor agents, *58*:35
synthesis of peptide analogs of, *58*:21
tissue disposition of, in the rat, monkey, and dog, *59*:1061
treatment of metastatic Ewing's sarcoma with, *54*:103
Actinomycins
clinical use of, *58*:121
controlled biosynthesis of, *58*:83
history and chemistry: molecular modification of, *58*:9
monolactones: origin and importance, *58*:93
origins of base specificity in, and other DNA ligands, *58*.97
possible approaches to further studies of, *58*:79
potential of, in cancer control, *58*:81
Adenocarcinoma
Aeromonas hydrophila peritonitis after chemotherapy in, *57*:489
clinical pharmacology of oral and iv 5–FU in disseminated, *58*:723
five-drug combination chemotherapy for, *56*:761
hexamethylmelamine in the treatment of, *56*:505
hydroxyurea intermittent therapy in, *53*:385
treatment with hexestrol, *52*:751
treatment with vincristine, *52*:733
Adenocarcinoma 755 *see* Tumor systems in animals, Carcinoma 755
ADJ/PC6A tumor *see* Tumor systems in animals, ADJ/PC6A tumor
Adjuvant therapy *see* Clinical studies
Adriamycin (NSC–123127)
alternating with the combination of vincristine and actinomycin D in the treatment of advanced sarcomas, *59*:1035
a new antibiotic with antitumor activity, *53*:33
antitumor activity and cardiotoxicity of, another hypothesis, *59*:258
biologic activity of, in microbial systems, *55*:221
cardiac uptake of, not affected by strophanthin G, *59*:765
combined with DTIC in the treatment of advanced, childhood, stage IV neuroblastoma, *59*:1015
compared with daunorubicin against mouse mammary carcinoma, *56*:153
compared with daunorubicin in the treatment of late-stage childhood solid tumors, *58*:671
compared with 5–FU plus cyclophosphamide in the treatment of advanced prostatic cancer, *59*:203
compared to 5–FU in the treatment of advanced colorectal cancer, *59*:405
compared with 5–FU in the treatment of advanced prostatic cancer, *59*:215
comparison of antileukemic effect of, with daunorubicin, *54*:1
contact dermatitis associated with, *59*:677

controlled evaluation of, in patients with disseminated breast cancer, *58*:877
cross resistance between vinca alkaloids and anthracyclines in Ehrlich ascites tumor in vivo, *56*:701
development of resistance to, in Ehrlich ascites tumor in vivo, *56*:321
derivatives, biologic activity of, *58*:769
effect of temperature on drug uptake by leukemic leukocytes in vitro, *59*:985
enhancement of the effectiveness of, against early mouse L1210 leukemia with ICRF–159, *59*:689
evaluation in the C1300 murine neuroblastoma model, *59*:975
hypotheses concerning antitumor activity and cardiotoxicity, *58*:293
in the treatment of acute myelocytic leukemia, *56*:237
new model for studying the effects of, on the growth of the prostate gland in rats, *59*:185
on the reported lack of effectiveness of, on solid tumors, *56*:431
pharmacokinetics of, in patients with sarcomas, *58*:271
phase I study, combined with 5–FU in the treatment of breast cancer and other solid tumors, *59*:1163
plus bleomycin in adult malignancies, *57*:413
plus CCNU in the treatment of solid tumors, *57*:437
plus cyclophosphamide and vincristine in the treatment of metastatic neuroblastoma, *58*:365
plus cyclophosphamide: a phase I and II evaluation, *58*:919
plus DTIC and vincristine in the treatment of metastatic sarcoma, *58*:265
plus DTIC, central nervous system complications after treatment with, *58*:753
plus methotrexate, cyclophosphamide, and 5–FU for adult solid tumors, *58*:943
plus prednisone or vincristine in metastatic mammary carcinoma, *58*:251
preliminary pharmacokinetic model for, *59*:819
some determinants of the therapeutic efficacy of, *58*:55
toxicity: unusual melanotic reaction, *58*:749
toxicologic screening in rats, *59*:707
in the treatment of advanced gastrointestinal cancer, *59*:405
in the treatment of alkylator-resistant multiple myeloma, *59*:345
treatment of Ewing's sarcoma with, *56*:635
treatment of MAC–13 and MAC–15, adenocarcinomas of the colon in mice, *59*:1083
in the treatment of metastatic melanoma, *59*:1181
uncommon side effects of, *58*:757
used in potential test systems in animals to determine activity against prostatic carcinoma, *59*:175

Adriamycin-DNA (NSC–169534), comparison of different formulations, *59*:260

Adriamycin, 14-octanoate, hydrochloride (NSC–149584), toxicologic screening in rats, *59*:707

Adverse reactions
adriamycin toxicity: unusual melanotic reaction, *58*:749
Aeromonas hydrophila peritonitis after chemotherapy, *57*:489
allergic reaction to daunorubicin, *54*:475
cardiotoxicity
of daunorubicin and adriamycin, another hypothesis of, *59*:258
of 5–FU in man, *59*:1051
central nervous system complications after combination treatment with adriamycin plus DTIC, *58*:753
cerebellar ataxia during 5–FU therapy, *55*:595
clinical, radiologic, and histopathologic studies on pulmonary toxicity induced by treatment with bleomycin, *56*:343
contact dermatitis associated with adriamycin and daunorubicin, *59*:677
development of herpes zoster in a patient with acute leukemia after therapy with cytosine arabinoside, *53*:49
effects of *cis*-dichlorodiammineplatinum(II) on hearing function in man, *58*:871
hypoalbuminemic and hypocholesterolemic effect of L-asparaginase treatment in man, *53*:67
immediate cerebral symptoms during rapid iv administration of cyclophosphamide, *59*:441
increased clinically symptomatic pulmonary radiation reactions with adjuvant chemotherapy, *58*:705
myocardial infarction as a possible complication of treatment with VP–16–213, mediastinal irradiation, or both, *59*:887
nephrotoxicity of streptozotocin, *54*:457
nonketotic hyperglycemia due to prednisone following ketotic hyperglycemia due to L-asparaginase plus prednisone, *56*:781
oropharyngeal sensation associated with rapid iv administration of cyclophosphamide, *56*:779
orthostatic hypotension during combination chemotherapy with vincristine, *58*:927
photosensitization of pseudourea, *55*:525
phototoxicity studies of pseudourea, *55*:91
physical activity: a possible determinant of vincristine neuropathy, *58*:413
possible inhibitory effect of androgens on bone marrow suppression by cytotoxic agents—a dose-dependent phenomenon?, *58*:125
possible radiation pericarditis in Hodgkin's disease, *54*:199
pulmonary cysts—a complication in combined chemotherapy for Wilms' tumor, *50*:319
recurrent masses at sites of prior Krebiozen injections, *58*:249
renal dysfunction after treatment with isophosphamide, *58*:375
reversible penile calcifications associated with bleomycin-induced pulmonary toxicity, *59*:1039
severe tumor pain with iv injection of vinblastine, *50*:281
uncommon side effects of adriamycin, *58*:757
vasculitis and blindness after intracarotid injection of BCNU in dogs, *57*:33
vocal cord paralysis: a toxic reaction to vinblastine therapy, *55*:591

Aeromonas hydrophila peritonitis after chemotherapy in adenocarcinoma, *57*:489

AH13 hepatoma *see* Tumor systems in animals, hepatoma

AH60C hepatoma *see* Tumor systems in animals, hepatoma
AH7974 hepatoma *see* Tumor systems in animals, hepatoma
AKR spontaneous leukemia (AKR lymphoma) *see* Tumor systems in animals, leukemia, AKR (lymphoma, AKR)
Alanine mustard (NSC–17663), phase II study of, *54*:361
Alkylating agents *see also* Names of
anticancer activity of, derived from various diamines and diols on Ehrlich ascites carcinoma, *51*:205
oncolytic effect of four C-16 aziridine steroidal, *51*:431
Allograft reaction, effect of *cis*-dichlorodiammineplatinum(II) on the, in mice, *58*:633
Allopurinol (NSC–1390)
clinical efficacy and lack of toxicity of, given iv, *54*:125
iv, in pediatric neoplasia, *58*:737
plus 6-mercaptopurine during remission of acute leukemia in children, *53*:53
Aluminum nitrate (NSC–143017), toxicity and antitumor activity in experimental rodent tumors, *59*:599
Amethopterin *see* Methotrexate
Amino acid derivatives (A-91, A-144, A-145, A-192, A-195), antitumor activity of, against various experimental tumor systems, *59*:309
2-Amino-4′-bis(5-methyl-2-imidazolin-2-yl)terephthalanilide *see* Terephthalanilide, 2-amino-4′,4″-bis(5-methyl-2-imidazolin-2-yl)-
L-(αS,5S)-α-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid (NSC–163501), a new amino acid antibiotic with the properties of an antagonist of L-glutamine, as an inhibitor of mammalian and bacterial reactions, *59*:481
antimicrobial reversal studies and preliminary evaluation against L1210 mouse leukemia in vitro, *57*:141
inhibition of L-asparagine synthetase by, *58*:793
(αS,4S,5R)-α-amino-3-chloro-4-hydroxy-4,5-dihydro-5-isoxazoleacetic acid (NSC–176324)
inhibition of L-asparagine synthetase by, *58*:793
preliminary evaluation against L1210 mouse leukemia in vivo, *58*:935
1-Aminocyclopentanecarboxylic acid *see* Cycloleucine
6-Aminonicotinamide (NSC–21206), evaluation of, in the treatment of metastatic hypernephroma, *54*:175
Aminopterin (NSC–739), plus deuterium oxide in chemotherapy on transplantable mouse tumors, *50*:641
3(or 5)-Aminopyrazole-4-carboxamide (NSC–1402), increased immunogenicity of murine lymphatic tumors by, *57*:3
Ammonium, trimethylpurin-6-yl chloride (NSC–51095)
cardiovascular effect of, in anesthetized dogs, *53*:99
further clinical studies of, in malignant disease with special emphasis on cancer of the urinary bladder, *51*:181
phase I study of, in advanced cancer, *52*:417
Amygdalin MF (NSC–15780, laetrile)
antitumor activity of, as a single agent and with β-glucosidase on a spectrum of transplantable rodent tumors, *59*:939
experimental studies of the antitumor activity of, alone and combined with β-glucosidase, *59*:951
Androgens, prediction of breast cancer response to, *58*:513
2,2′-Anhydro-1-(β-D-arabinofuranosyl)cytosine hydrochloride (NSC–145668), synthesis and biologic examination of some derivatives of, *58*:451
Anhydro-ara-C (NSC–129220), studies of the L1210 antileukemic activity of, compared with cytosine arabinoside with respect to treatment schedule dependency, *56*:483
Anhydro-ara-5-fluorocytidine (NSC–166641), evaluation of sialologic action, *59*:1019
-α-Anilino-α-toluenesulfonic acid *see* α-Toluenesulfonic acid, α-anilino-
Anticancer agents, structure-activity correlations of: diaminopyrimidines, *N*-acyltriamines, bis-(1-aziridinyl)-phosphinyl carbamates, and aromatic nitrogen mustards, *57*:251
Antimetabolites
experimental approaches to cancer chemotherapy involving combinations of metabolites and, *58*:471
mechanism of action of antitumor antibiotic inhibitors of protein synthesis, *58*:479
Antiviral agents, in vivo properties of biologically active compounds, studies with Friend leukemia virus, *50*:299
Antiviral chemotherapy, as an adjunct to cancer chemotherapy, *59*:261
Arabinosylcytosine *see* Cytosine arabinoside
Ara-C *see* Cytosine arabinoside
L-Asparaginase (NSC–109229)
alone or plus prednisone, causing nonketotic or ketotic hyperglycemia, *56*:781
antitumor activity and other biologic properties of, a review, *52*:617
combined with other agents in the treatment of murine leukemias, *54*:329
distribution and mechanism of clearance of, *55*:539
effect on transplantable and spontaneous tumors from mice and rats, *53*:189
failure of combination therapy with *S*-carbamyl-L-cysteine and, for L-asparaginase-resistant mouse lymphoma, *56*:339
hypoalbuminemic and hypocholesterolemic effect of, in man, *53*:67
induction and characteristics of resistance to, in mouse leukemia L5178Y, *55*:115
pharmacologic studies in man with crystallized, *56*:611
plus azaserine in acute lymphatic leukemia, *54*:47
plus cytosine arabinoside, effective treatment of advanced acute lymphocytic leukemia, *56*:363
treatment of adult leukemia with, *55*:269
L-Asparagine synthetase, inhibition of, by an amino acid antitumor antibiotic, L-(αS,5S)-α-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid, *58*:793
Assay techniques
assay for citrovorum factor in the presence of methotrexate, *59*:935
chemical assay to determine concentrations of inosine dialdehyde in biologic fluids, *59*:685
microbiologic assay for cytosine arabinoside, using a mutant of *Streptococcus faecium* var. *durans* resistant to methotrexate and 6-MP, *59*:515
new in vitro method for assaying colony-forming cells of Lewis lung carcinoma and B16 melanoma, comparison of effects of three nitrosoureas, *59*:929

a useful biologic assay for tetrahydrouridine, a potent inhibitor of cytosine arabinoside deamination, *59*:717
Astrocytoma, treatment of, with CCNU, *55*:99
Autoimmunity, oncocognitive, *58*:441
Avian myeloblastosis virus *see* Oncogenic viruses
5-Azacytidine (NSC–102816)
absorption, distribution, and excretion of, in man, *56*:405
alone or with subsequent use of cyclophosphamide in the treatment of breast cancer, *58*:677
clinical trial with sc administered, *58*:217
combined with methyl-GAG in previously treated adults with acute nonlymphocytic leukemia, *59*:1043
enhancement by tetrahydrouridine of the oral activity of, in L1210 leukemic mice, *59*:459
kinetics of the reduction in viability of cultured L1210 leukemia cells exposed to, *56*:585
phase I study of, *56*:413
phase I study of twice weekly, *58*:899
phase II study of, in the treatment of advanced gastrointestinal cancer, *56*:649
phase I study of, using a 24-hour continuous infusion for 5 days in the treatment of various cancers, *59*:1123
treatment of acute leukemia with, *57*:319
8-Azaguanine (NSC–749), preclinical toxicity studies and a preliminary report on intrathecal perfusion therapy for patients, *50*:283
Azaserine (NSC–742)
combined with 6-thioguanine for multiple myeloma, *51*:234
plus L-asparaginase in acute lymphatic leukemia, *54*:47
plus 6-thioguanine in the treatment of terminal chronic myelocytic leukemia, *58*:233
6-Azauridine (NSC–32074)
chemotherapy for patients with leukemia, *53*:203
phase I study of, in solid tumors, *53*:79
Aziridines, oncolytic effect of four C-16 steroidal alkylating agents, *51*:431
Azotomycin (NSC–56654)
biologic fate in mice and man, *55*:47
phase I study of, plus 5-FU in colon carcinomas, *54*:109
phase II study of, *52*:611

B

Bacillus Calmette Guérin *see* BCG
Basal cell carcinoma *see* Carcinoma in man, basal cell
BCG
for prostatic cancer in man, *59*:251
immunotherapy of prostatic cancer with, *59*:157
prevention of cyclophosphamide immunosuppression by, *58*:931
regression of intradermal malignant melanoma after intralesional injection of *Mycobacterium bovis* strain, *56*:659
BCNU (NSC–409962)
activity against human tumor xenografts in immune-deprived mice, *58*:645
alone or combined with cyclophosphamide in patients with inoperable or disseminated lung cancer, *56*:401
alone or combined with cytosine arabinoside or methotrexate in the treatment of advanced solid tumors, *56*:751
analysis of the effects of, on cell cycle kinetics, *59*:847
combined with cyclophosphamide in the remission maintenance of adult acute nonlymphocytic leukemia, *59*:537
compared to methyl-CCNU and CCNU with regard to sensitivity of colony-forming cells of hemopoietic tissue, Lewis lung carcinoma, and B16 melanoma, *59*:929
comparison of postoperative irradiation alone or combined with, in the management of malignant gliomas, *58*:841
effect of, alone or combined with levamisole, on DNA synthesis by lymphocytes from immunosuppressed C57BL mice, *59*:531
effect of, on kinetic behavior of cultured L1210 leukemic cells, *51*:7
effect of, on NAD glycohydrolase in normal and leukemic mouse tissues, *52*:569
effects on progression of L1210 cells through the cell cycle, *55*:215
evaluation in the C1300 murine neuroblastoma model, *59*:975
in the management of patients with advanced breast cancer, *56*:93
in the treatment of advanced Hodgkin's disease, lymphosarcoma, and reticulum cell sarcoma, *58*:383
in the treatment of brain tumors, *54*:273
in the treatment of bronchogenic carcinoma, *56*:739
in the treatment of malignant brain tumor, *54*:263
L1210 leukemia cell death in vivo after administration of, *53*:273
microbiologic evaluation and assay, *51*:213
phase II clinical trials of, in the treatment of Kaposi's sarcoma, *57*:325
phase II evaluation of, in patients with solid tumors, *56*:787
phase II study of, in the treatment of bronchogenic carcinoma, *56*:259
plus cyclophosphamide for advanced solid tumors, *56*:53
plus cyclophosphamide in bronchogenic carcinoma, *58*:883
plus cytosine arabinoside and prednisone in the treatment of terminal chronic myelocytic leukemia, *58*:233
plus cytosine arabinoside, DTIC, and methotrexate in advanced L1210 leukemia, *57*:291
plus cytosine arabinoside in the treatment of cancer, *55*:347
plus cytosine arabinoside in the treatment of Sarcoma 180 and L1210 leukemia in vivo, *53*:215
plus 5-FU, DTIC, and vincristine given concomitantly in the treatment of solid tumors in man, *56*:107
plus 5-FU for disseminated gastrointestinal cancer, *56*:653
plus fluoxymesterone in the treatment of solid tumors, *57*:225
plus surgery on an animal brain tumor model, *58*:627
plus vincristine in disseminated gastrointestinal cancer and other neoplasms, *58*:947
response of advanced breast cancer to two dosage regimens of, *57*:231

toxicity study of, given orally, *58*:407
treatment of Hodgkin's disease and other cancers with, *55*:599
treatment of MAC–13 and MAC–15, adenocarcinomas of the colon in mice, *59*:1083
vasculitis and blindness after intracarotid injection of, in dogs, *57*:33
BIC (NSC–82196)
clinical experience with, in the treatment of metastatic malignant melanoma, *56*:671
clinical trials and pharmacologic studies with, given orally, *55*:159
clinical trials with, given iv, *56*:387
colorimetric determination in blood, *53*:199
comparative studies on the chemical stability and therapeutic effectiveness of water-insoluble, and its water-soluble hydrochloride against L1210 leukemia in mice, *57*:383
comparison of the cytotoxicity of, on normal and leukemic colony-forming cells, *55*:43
effectiveness of antileukemic agents in mice inoculated with an L1210 leukemia variant resistant to, *53*:229
effectiveness of antileukemic agents in mice inoculated with L1210 leukemia variants resistant to, *55*:9
in the treatment of childhood malignancy, *59*:371
influence of treatment schedules and routes of administration on the chemotherapy of murine L1210 leukemia with, *52*:715
kinetics of the effect of, on the reproductive integrity of cultured L1210 leukemia cells, *52*:725
phase II clinical trial of, in primary and secondary brain tumors, *59*:327
phase II study of, in advanced gastrointestinal cancer, *56*:267
plus CCNU in patients with various disseminated solid tumors, *59*:769
spleen colony studies of L1210 leukemia, sensitivities of L1210 and L1210/6–MP to, *52*:393
Biopsy, determination of sensitivity of individual specimens of, to potential inhibitory agents: evaluation of some explant culture methods as assay systems, *50*:543
4,4′ Biphenyldisulfonic acid compounded with 3,3′-(methylamino)di-1-propanol, dimethanesulfonate (ester) (NSC–140115), in the treatment of malignant lymphoma, *57*:159
3-[Bis(2-chloroethyl)amino]-4-methylbenzoic acid (NSC–146171), in vitro and in vivo cytogenetic effects of, in human peripheral leukocytes, *57*:29
[*p*-[Bis(2-chloroethyl)amino]phenyl]acetic acid (NSC-71964), homo-aza-steroidal ester, antitumor activity of, in animals, *57*:365
1,3-Bis(2-chloroethyl)-1-nitrosourea *see* BCNU
5-[3,3-Bis(2-chloroethyl)-1-triazeno]imidazole-4-carboxamide *see* BIC
Bladder cancer *see* Carcinoma in man, bladder
Bleomycin (NSC–125066)
alone or in combination with CCNU in the treatment of metastatic testicular cancer, *59*:429
clinical radiologic and histopathologic studies on pulmonary toxicity induced by treatment with, *56*:343
combined with CCNU in the treatment of MOPP-resistant Hodgkin's disease, *59*:1147
combined with vincristine and methotrexate plus radiation therapy in the treatment of non-oat-cell bronchogenic cancer, *59*:377
continuous iv therapy combined with vinblastine in stage III testicular neoplasia, *59*:563
evaluation in the C1300 murine neuroblastoma model, *59*:975
failure of Indium 111-labeled bleomycin tumor scanning to predict response to treatment with, *58*:733
in the treatment of advanced epidermoid carcinoma of the uterine cervix, *57*:429
in the treatment of metastatic liver cancer, *59*:433
in vitro screening of, *57*:463
phase I clinical study, *56*:197
phase II clinical trials of, in the treatment of Kaposi's sarcoma, *57*:325
phase II study of, therapy for large bowel cancer, *56*:207
plus adriamycin in adult malignancies, *57*:413
plus dibromodulcitol, effect on squamous cell carcinoma in man, *56*:625
plus vincristine in patients with lung cancer and other malignant tumors, kinetic scheduling of, *57*:219
plus vincristine therapy for disseminated testicular tumors, *58*:213
pulmonary fibrosis following multiple treatment with, in dogs, *58*:301
pyrogenic properties of, *57*:393
reversible penile calcifications associated with pulmonary toxicity induced by, *59*:1039
treatment of advanced squamous cell carcinoma of the gastrointestinal tract with, *57*:493
used in potential test systems in animals to determine activity against prostatic cancer, *59*:175
Body surface area, estimation of human, from height and weight, *54*:225
Bone marrow cells, determination of therapeutic index of drugs by-in vitro sensitivity of *57*:11
Bone marrow suppression, effect of nandrolone phenylpropionate on, caused by cyclophosphamide, *58*:867
Bone marrow transfusions, effect of testosterone enanthate on erythropoiesis in irradiated mice given, *52*:627
Brain cancer *see* Carcinoma in man, brain
Breast cancer *see* Carcinoma in man, breast
Bretylium tosylate (NSC–62164), unorthodox therapy for murine neuroblastoma with, *59*:571
2-Bromo-α-ergocryptine (NSC–169774), clinical trial in the treatment of human prostatic cancer, *59*:209
Bronchial carcinoma *see* Carcinoma in man, lung
Bronchogenic carcinoma *see* Carcinoma in man, lung
Burkitt's lymphoma
CCNU used for the prevention of central nervous system involvement in, *59*:1155
potential biologic markers in, *59*:721
treatment with cyclophosphamide in, *51*:397
Busulfan (NSC–750)
clinical trial of, in advanced carcinoma of the prostate, *51*:295
treatment, followed by dibromomannitol in patients with refractory chronic myelocytic leukemia, *58*:223
1,3-Butanediol cyclic sulfite (NSC–60195)
effect of, on lactate dehydrogenase, *50*:85
inhibition of lactate dehydrogenase by, *50*:89

physiologic disposition of, given orally to rats, *52*:337
Butocin (NSC–172755), preliminary clinical trials of, in patients with generalized carcinoma of the breast, *57*:311
Butyraldehyde, 3-ethoxy-2- oxo-bis(thiosemicarbazone) (NSC–82116)
activity of combinations of uracil mustard and, against murine tumors, *50*:557
clinical pharmacologic study of, in advanced cancer, *51*:171
Butyric acid (NSC–8415), unorthodox therapy for murine neuroblastoma, *59*:571

C

Calusterone (NSC–88536)
antitumor activity of, in advanced breast cancer, *59*:890
poor substitute for fluoxymesterone in the treatment of advanced breast cancer, *58*:939
Camptothecin (NSC–100880)
fluorometric method for determination of, in plasma and urine, *53*:211
pharmacologic studies of: distribution, plasma protein binding, and biliary excretion, *57*:125
phase I clinical trials of weekly and daily treatment with, correlation with preclinical studies, *56*:515
phase II study of, in the treatment of advanced gastrointestinal cancer, *56*:94
pharmacologic and clinical evaluation of, *54*:461
plasma levels during a 5-day course of treatment: relation to dose and toxicity, *56*:573
renal clearance of: effect of urine volume, *57*:175
treatment of malignant melanoma with, *56*:103
Cancer Chemotherapy Program of the National Cancer Institute, objectives, analysis, and accomplishments, *50*:397
S-carbamyl-L-cysteine (NSC–102498), failure of combination therapy with L-asparaginase for L-asparaginase-resistant mouse lymphoma, *56*:339
Carbazilquinone (NSC–134679)
clinical experience with, *57*:447
increased lifespan using the priming dose schedule design in treatment of mouse L1210 leukemia, *56*:19
Carbestrol (NSC–19962), phase II study of, in patients with solid tumors, *56*:641
4-Carbethoxy-5-(3,3-dimethyl-1-triazeno)-2-methylimidazole (NSC–166722), evaluation of, as a potential antitumor agent, *57*:263
4-Carbethoxy-5-(3,3-dimethyl-1-triazeno)-2-phenylimidazole (NSC–166721), evaluation of, as a potential antitumor agent, *57*:263
***p*-Carboxycarbanilic acid, *N*-[*p*-[bis(2-chloroethyl)amino]-phenyl] ester (NSC–130998, IC 140)**, antitumor and toxicologic effects of, *54*:23
Carcinogenesis
cancer chemotherapeutic agents and, *59*:915
hazard of lymphography, *52*:77
Carcinogens, renal action of streptozotocin in rats, *52*:563
Carcinoid syndrome, malignant: effect of parenteral methotrexate alone and combined with cyclophosphamide orally, *51*:239
Carcinoma 755 *see* Tumor systems in animals
Carcinoma in man
basal cell, therapy of, with local applications of vitamin A acid, *55*:59
bladder, ammonium, trimethylpurin-6-yl chloride in the treatment of, *51*:81
brain
BCNU in the treatment of, *54*:263,273
chemotherapeutic response of, cells cultured in cerebrospinal fluid, *51*:201
comparison of postoperative irradiation alone and in combination with BCNU in the management of, *58*:841
intrathecal methotrexate therapy for, in children, *52*:257
microculture of, *54*:9
phase II study of CCNU in the treatment of, *56*:421
phase II study of methyl-CCNU, *59*:1022
primary and secondary, phase II clinical trial of BIC in, *59*:327
transplanted, intrathecal injection of methotrexate in, *51*:1
treatment of, with CCNU, *55*:99
breast
adriamycin plus CCNU in the treatment of, *57*:437
advanced, antitumor activity of calusterone in the treatment of, *59*:890
advanced, antitumor efficacy and toxicity of methyltrienolone in, *54*:453
advanced, calusterone, a poor substitute for fluoxymesterone, *58*:939
advanced, chlorambucil treatment in patients with, *52*:661
advanced, cyclophosphamide combined with cytosine arabinoside and methotrexate in the treatment of, *59*:1091
advanced, five-drug therapy for, *55*:183
advanced, mitomycin C treatment in patients with, *52*:675
advanced, phase II trial of isophosphamide in patients with, *58*:861
advanced, preliminary clinical trial of DL-metasarcolysin for, *52*:413
advanced, response of, to two dosage regimens of BCNU, *52*:231
advanced, Δ^1-testololactone, massive doses of, *50*:323
BCNU in the management of, *56*:93
clinical trial with sc administered 5–azacytidine, *58*:217
combination chemotherapy for, *59*:893
combinations of cyclophosphamide, vincristine, and 5–FU in the treatment of, *59*:425
comparison of 5–azacytidine with CCNU in patients with, and evaluation of the subsequent use of cyclophosphamide, *58*:677
comparison of monthly courses versus weekly doses of 5–FU, *53*:243
comparison of Δ^1–testololactone and Deluteval 2x in, *54*:249
cis-dichlorodiammineplatinum(II) alone and in combination in the treatment of, *59*:647

disseminated, controlled evaluation of adriamycin in patients with, *58*:877
disseminated, 5–FU given by the multiple daily dose method in, *51*:483, *57*:59
dromostanolone propionate in the treatment of, *56*:89
effect of massive doses of estradiol undecylate in, *51*:491
five-drug combination chemotherapy for, *56*:761
5–FU, DTIC, vincristine, and BCNU given concomitantly in the treatment of, *56*:107
hexestrol, treatment with, *52*:751
melphalan in the treatment of, *50*:271
metastatic, clometherone therapy for, *50*:327
metastatic, combination chemotherapy with adriamycin, *58*:251
metastatic, treatment of, with combination of hormones and other chemotherapy, *52*:743
7-α-methyl-19-nortestosterone in the treatment of, *50*:335
new adjuvant therapy for, *51*:167
phase I and II studies of 2′-deoxy-5-(trifluoromethyl)uridine, *55*:205
phase I study of 5–azacytidine in patients with, *56*:413
phase I study of 5–FU plus adriamycin in the treatment of, *59*:1163
phase I study of phenesterin, *55*:259
phase II study of dibromodulcitol, *58*:653
prediction of response to endocrine therapy, *58*:513
preliminary clinical trials of butocin in patients with, *57*:311
private practice of medical oncology in, *58*:759
renal dysfunction after treatment with isophosphamide for, *58*:375
VP–16–213 given orally in the treatment of, *59*:1027

cervical
advanced, chlorambucil treatment in patients with, *52*:661
disseminated squamous, porfiromycin in the treatment of, *53*:305
further experience with hexamethylmelamine in the treatment of, *57*:497
hydroxyurea with irradiation for, *52*:601
methotrexate and bleomycin in the treatment of advanced epidermoid, *57*:429
porfiromycin in the treatment of, *56*:615
treatment of, by methotrexate plus cyclophosphamide, *53*:255

colon
advanced, mitomycin C plus 5–FU and cytosine arabinoside for, *56*:373
advanced, mitomycin C treatment in patients with, *52*:675
comparative response of carcinoma of the rectum and, to fluorinated pyrimidines, *53*:283
development of a method for assessing antitumor activity of chemotherapeutic agents using, xenograft, *58*:645
cis-dichlorodiammineplatinum(II) treatment in advanced, *57*:357
comparison of mitomycin C and 5–FU using hepatic arterial infusion for liver metastases resulting from, *59*:401
effect of resection of the primary neoplasm on responsiveness to chemotherapy of patients with large bowel cancer, *56*:551
5–FU, DTIC, vincristine, and BCNU given concomitantly in the treatment of, *56*:107
metastatic, phase II trials with procarbazine, streptozotocin, 6–thioguanine, or CCNU in patients with, *59*:333
100% oxygen inhalation and 5–FU therapy for, *58*:951
phase I study of azotomycin plus 5–FU in, *54*:109
phase II study of bleomycin therapy for, *56*:207
phosphoribosyl transferase in, as an aid to adjuvant chemotherapy with 5–FU, *58*:909
porfiromycin in the treatment of, *56*:615
vincristine plus 5–FU in the treatment of, *59*:425

colorectal
advanced, phase II study of ICRF–159 in, *59*:761
advanced, phase II study of cytembena in, *59*:581
advanced, phase II study of chromomycin A_3 in, *59*:577
advanced, adriamycin in the treatment of, *59*:405
clinical studies of mitomycin C in, *53*:287
comparison of monthly courses versus weekly doses of 5–FU, *53*:243
treated with 5–FU, *56*:563

connective tissue, advanced, chlorambucil treatment in patients with, *52*:661

determination of therapeutic index of drugs by in vitro sensitivity tests, *57*:11

epithelial, phase I evaluation of cyclocytidine in the treatment of, *59*:389

esophageal, methyl-GAG in the treatment of, *55*:209

gastrointestinal
advanced, comparative evaluation of palliation with fluorometholone and 5–FU alone or in combination, *51*:77
advanced, methyl-CCNU alone or in combination with cyclophosphamide in the treatment of, *59*:1161
advanced, phase II study of 5–azacytidine in the treatment of, *56*:649
advanced, phase II study of camptothecin in the treatment of, *56*:94
advanced, phase II study of CCNU in, *58*:667
advanced, phase II study of streptozotocin in the treatment of, *55*:303
advanced, squamous cell carcinoma, treated with bleomycin, *57*:493
combination therapy with 5–FU and BCNU for disseminated, *56*:653
5-day iv infusion with 5–FU after weekly 5–FU failure, *59*:1177
cis-dichlorodiammineplatinum(II) alone and in combination in the treatment of, *59*:647
disseminated, BCNU plus vincristine in, *58*:947
DTIC in patients with, *54*:471
effect of concomitant drug treatment on toxic and therapeutic activity of 5–FU, *56*:245
effect of patient selection on results of chemotherapy trials in, *58*:257
phase II study of BIC in advanced, *56*:267
phase II study of methyl-CCNU, *59*:1021

streptonigrin by continuous iv infusion in the treatment of advanced, ***51***:73
treatment of, with emetine, ***58***:229
VP–16–213 given orally in the treatment of, ***59***:1027
genitourinary
cis-dichlorodiammineplatinum(II) alone and in combination in the treatment of, ***59***:647
VP–16–213 given orally in the treatment of, ***59***:1027
head and neck
advanced, treated with high-dose infusions of methotrexate plus radiotherapy, ***56***:745
cis-dichlorodiammineplatinum(II) in the treatment of, ***59***:621
epidermoid, cytosine arabinoside in the treatment of, ***55***:193
malignant schwannoma, vincristine plus cyclophosphamide for generalized, ***54***:65
phase II study of methyl-CCNU, ***59***:1021
porfiromycin in the treatment of, ***56***:615
squamous cell, methotrexate in, intermittent iv therapy, ***51***:69
toxicity of 24-hour infusions of methotrexate and protection by citrovorum factor in patients with epidermoid carcinomas, ***51***:305
kidney, metastatic, vincristine combined with hydroxyurea in the treatment of, ***59***:1159
large bowel *see* Carcinoma in man, colon
last surviving cancer cell: the chances of killing it, ***50***:541
lip, residual or relapsing, 5–FU applied in a mouthwash in the topical treatment of, ***59***:1052
liver
clinical trials with dichloromethotrexate in, ***56***:249
hepatoma, combination of 5–FU, methotrexate, and prednisolone in the treatment of, ***59***:1167
metastatic, clinical trial of bleomycin in the treatment of, ***59***:433
lung
advanced, CCNU in the treatment of, ***58***:421
advanced, cyclophosphamide combined with cytosine arabinoside and methotrexate in the treatment of, ***59***:1091
advanced, procarbazine in the treatment of, ***53***:135
advanced, procarbazine plus 5–FU in, ***54***:369
advanced, randomized study comparing CCNU and methyl-CCNU, ***58***:913
antitumor activity of 1-methyl-1-nitrosourea, ***58***:135
BCNU in the treatment of, ***56***:739
bronchial artery infusion in, ***52***:263
chemotherapeutic response and iv hyperalimentation in, ***59***:437
comparison of two dose schedules of dichloromethotrexate in, ***57***:79
continued studies of combined chemotherapy and irradiation in inoperable, ***51***:189
criteria for resection of sarcoma metastatic to, ***58***:285
cyclophosphamide in the treatment of, ***59***:411
disseminated or inoperable, cyclophosphamide and BCNU, alone or in combination in patients with, ***56***:401
DTIC in the treatment of, ***55***:83
epidermoid, phase I–II studies of emetine in the treatment of, ***59***:1171
5–FU compared to cyclophosphamide in the treatment of, ***59***:1025
heparin in the treatment of, ***56***:783
hexamethylmelamine in the treatment of, ***56***:505
hexamethylmelamine plus methotrexate in the treatment of, ***55***:299
importance of dose schedules in adjuvant chemotherapy, ***56***:35
intermittent parenteral methotrexate therapy for, ***51***:475
kinetic scheduling of vincristine and bleomycin in patients with, ***57***:219
methyl-CCNU in the treatment of, ***57***:419
non-oat-cell, bleomycin, vincristine, and methotrexate plus radiation therapy in the treatment of, ***59***:377
nonresectable, hydroxyurea in therapy for, ***52***:271
nonresectable, treatment of, with hydroxyurea given intermittently, ***55***:87
nonresectable, treatment of, with various agents, ***58***:359
phase I study of guanazole in, ***59***:1117
phase I study of thalicarpine in, ***59***:1001
phase II study of BCNU in the treatment of, ***56***:259
phase II study of dibromodulcitol in, ***58***:653
phase II study of methyl-CCNU in, ***59***:1021
radiation plus 5–FU: clinical demonstration of an additive effect in, ***55***:253
small cell, effect of hexamethylmelamine on, phase II study, ***58***:371
small cell, methyl-CCNU, cyclophosphamide, and vincristine in the treatment of, in a 3–week schedule, ***59***:1127
treatment of, with 1-acetyl-2-picolinoylhydrazine, ***54***:243
treatment of, with cyclophosphamide plus BCNU, ***58***:883
trials with NSC–140117, a methanesulfonic acid ester of aminoglycol, ***59***:367
vinblastine in the treatment of, ***54***:451
VP–16–213 given orally in the treatment of, ***59***:1027
VP–16–213 in the treatment of, ***59***:737
ovary
advanced, meturedepa treatment in patients with, ***52***:667
chlorambucil treatment in patients with advanced, ***52***:661
clinical trial with sc administered 5–azacytidine, ***58***:217
combinations of cyclophosphamide, vincristine, and 5–FU in the treatment of, ***59***:425
cis-dichlorodiammineplatinum(II) in the treatment of, ***59***:621
intermittent high-dose cyclophosphamide treatment of stage III, ***58***:689
hexamethylmelamine in the treatment of, ***56***:505
metastatic and advanced, 6-dehydro-6,17-α-dimethylprogesterone for the treatment of, ***57***:241
phase II study of methyl-CCNU, ***59***:1021

recurrent or progressive, high-dose cyclophosphamide in the treatment of, *59*:157
pancreas
combinations of cyclophosphamide, vincristine, and 5–FU in the treatment of, *59*:425
5–FU in the treatment of: comparison of oral and iv routes, *59*:1031
prostatic
advanced, busulfan in the treatment of, *51*:295
advanced, comparison of adriamycin and the combination of 5–FU and cyclophosphamide in the treatment of, *59*:203
advanced, comparison of 5–FU and cyclophosphamide in the treatment of, *59*:195
advanced, comparison of adriamycin and 5–FU in the treatment of, *59*:215
advanced, stage D, oral estramustine phosphate in the treatment of, *59*:219
characterization of, among blacks, *59*:3
classification of, *50*:125
clinical trial of 2-bromo-α-ergocryptine in the treatment of, *59*:209
collection of postmortem prostate tissue under sterile conditions, *59*:91
cultivation of epithelial cells from the prostate to develop an immune cytotoxicity assay for, *59*:147
detection and diagnosis of: general discussion, *59*:151
detection of, *59*:139
disaggregation of prostates and purification of epithelial cells from normal and cancerous prostates using sedimentation in an isokinetic density gradient of Ficoll in tissue culture medium, *59*:143
effect of progestational agents on, *51*:41
etiology and prevention of, *59*:65,73,89
extended-field radiation therapy for, *59*:165
far-advanced, clinical results with estramustine phosphate: comparison of iv and oral preparations, *59*:229
grading of, *59*:111
immunotherapy of, with BCG, *59*:157
investigation of specific antigens in, *59*:105
monolayer cultures of human prostatic cells, *59*:59
neoplastic effect of 3–methylcholanthrene on human prostate in organ culture, *59*:67
potential screening agents for, *59*:119
potential test systems in animals to predict for activity against, *59*:175
review of clinical trials by the Veterans' Administration Cooperative Urological Research Group, *59*:225
search for virogene in, *59*:39
stage D, 5-FU versus CCNU and 5-FU plus diethylstilbestrol versus diethylstilbestrol alone in the treatment of, *59*:243
survival rates of patients with, tumor stage and differentiation, *50*:129
treatment for, using an exponential-life model relating survival to concomitant information, *58*:845
treatment of: general discussion, *59*:251
tumor antigen and acid phosphatase isoenzyme in, *59*:97
virologic and immunologic studies of, *59*:17
virology of, *59*:33
rectal, comparative response of, and carcinoma of the colon to fluorinated pyrimidines, *53*:283
reticulum cell, phase II study of methyl-CCNU, *59*:1021
squamous cell
bleomycin plus dibromodulcitol effect on, *56*:625
dibromodulcitol in the treatment of, *53*:377
cis-dichlorodiammineplatinum(II) alone and in combination with other agents in the treatment of, *59*:647
gastrointestinal tract, treatment of with bleomycin, *47*:493
head and neck cancer, toxicity of 24-hour infusions of methotrexate and protection by citrovorum factor in patients with, *51*:305
head and neck, cytosine arabinoside in the treatment of, *55*:193
head and neck, methotrexate in intermittent iv therapy for, *51*:69
intermittent intra-arterial infusion of 5-FU in outpatients with, *50*:331
of the cervix, porfiromycin for treatment of, *53*:305
treatment with vincristine, *52*:733
stomach
advanced, adriamycin in the treatment of, *59*:405
advanced, mitomycin C plus 5-FU and cytosine arabinoside for, *56*:373
clinical experience with the streptococcal anticancer preparation, OK–432, *56*:211
combinations of cyclophosphamide, vincristine, and 5-FU in the treatment of, *59*:425
importance of dose schedules in adjuvant chemotherapy, *56*:35
strategy for curing cancer, *50*:295
testicular
actinomycin D in the treatment of, *58*:49
cis-dichlorodiammineplatinum(II) in the treatment of, *59*:621
metastatic, bleomycin alone or combined with CCNU in the treatment of, *59*:429
metastatic, high-dose cyclophosphamide for the treatment of, *58*:709
stage III, continuous iv bleomycin therapy combined with vinblastine in, *59*:563
vinblastine plus bleomycin therapy for disseminated, *58*:213
uterine, *Aeromonas hydrophila* peritonitis after chemotherapy in, *57*:489
Carminomycin (NSC–180024), a new antibiotic, activity in experimental systems, *58*:255
CCNU (NSC–79037)
alone or with subsequent use of cyclophosphamide in the treatment of breast cancer, *58*:677
combined with bleomycin in the treatment of metastatic testicular carcinoma, *59*:429
combined with bleomycin in the treatment of MOPP-resistant Hodgkin's disease, *59*:1147
compared to methyl-CCNU and BCNU with regard to sensitivity of colony-forming cells of hemopoietic tissue, Lewis lung carcinoma, and B16 melanoma, *59*:929
compared with methyl-CCNU in advanced bronchogenic carcinoma, *58*:913

effect of, and its degradation products on progression of L1210 cells through the cell cycle, *55*:215
effect of, in sesame oil administered im in the treatment of experimental brain tumors, *56*:457
in the treatment of malignant brain tumors, *55*:99
new model for studying the effects of, on the growth of the prostate gland in rats, *59*:185
phase II study of, in the treatment of brain tumors, *56*:421
phase II trials with, in patients with metastatic cancer of the large bowel, *59*:333
plus adriamycin in the treatment of solid tumors, *57*:437
plus BIC in patients with various disseminated solid tumors, *59*:769
treatment in advanced nonhematologic cancer, *58*:421
treatment of advanced neoplastic disease with, *57*:201
treatment of MAC–13 and MAC–15, adenocarcinomas of the colon in mice, *59*:1083
used for the prevention of CNS involvement in Burkitt's lymphoma, *59*:1155
used in potential test systems in animals to determine activity against prostatic carcinoma, *59*:175
versus 5-FU in the treatment of stage D prostatic adenocarcinoma, *59*:243

CEA (carcinoembryonic antigen), in plasma and prostatic fluid from man, dog, and baboon, *59*:97

Cell division
cell cycle specificity and therapeutic effectiveness of cytostatic agents, *56*:691
cytotoxicity of antitumor agents in a synchronous mammalian cell system, *58*:149
in the design of optimal therapeutic schedules, *54*:431
kinetic parameters and growth curves for experimental tumor systems, *54*:143
sensitivity of resting cells and, *54*:137

Cell lines
blood clearance of, *55*:527
cell survival and repair of plateau-phase cultures after chemotherapy—relevance to tumor therapy and to the in vitro screening of new agents, *57*:473
chemotherapeutic response of epithelial tumors produced by primary implantation of a nonproducer line of murine sarcoma virus-transformed BALB/3T3 cells, *57*:149
chemotherapeutic response of human glial tumor cells cultured in cerebrospinal fluid, *51*:201
cytopathologic effects of mercenene on HeLa and human amnion (FL) cells, *50*:655
cytotoxicity of antitumor agents in a synchronous cell system, *58*:149
effect of mannitol mustard on nuclear DNA content, *53*:115
effect of pseudourea on DNA, RNA, and protein synthesis in cultured cells, *57*:399
development of sensitivity of individual, to potential inhibitory agents: evaluation of some explant culture methods as assay systems, *50*:543
further studies on selective cytotoxicity of Triton WR–1339, *52*:243
genetic alteration in tumor cells resulting in their escape from the immune response, *58*:431
interference with formation and expression of RNA tumor virus information: rationale and experimental results, *58*:579
nitroheterocyclic drugs as selective radiosensitizers of hypoxic mammalian, *58*:559
structure-cytotoxicity relations of some corticosteroids in L cells, *51*:225
ultrastructural studies on, treated with vincristine, *52*:509

Cell number, new technique for the measurement of ascites tumor, *58*:741

Cell survival, possible approaches to selective toxicity, new concepts in cancer chemotherapy, *51*:247

Cervical cancer *see* Carcinoma, cervical

Chemotherapy program of the National Cancer Institute
history of, *50*:349
policy statement on confidential compounds, *50*:385
proposals for future programs of, *55*:461

Chlorambucil (NSC–3088)
cytologic studies on human melanoma cells in tissue culture, *52*:543
effects of, in 374 patients with advanced cancer—Eastern Clinical Drug Evaluation Program, *52*:661
treatment of MAC–13 and MAC–15, adenocarcinomas of the colon in mice, *59*:1083

Chlorasquin (NSC–529861), dosage schedules in L1210 leukemia and toxicity, *55*:123

Chlormadinone acetate (NSC–92338), effect of, on carcinoma of the prostate, *51*:41

1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea *see* CCNU

3-*N*,*N*-bis(2-Chloroethylamino)*p*-toluic acid (NSC–146171), a new cytostatic drug active in cancer, *54*:319

6α-Chloro-16α-methylpregn-4-ene, 3,20-dione *see* Clometerone

Chloroquine (NSC–187208), combined with cyclophosphamide and prednisone in the treatment of multiple myeloma resistant to melphalan, *59*:557

Cholesterol
effect of L-asparaginase on blood levels of, in man, *53*:67
effect of cholesterol-free, fat-free diet, and hypocholesteremic agents on growth of transplantable animal tumors, *50*:25

Choriocarcinoma, actinomycin D in the treatment of, *58*:49

Chromomycin A_3 (NSC–58514)
phase I study of, *57*:341
phase II study of, in advanced colorectal cancer, *59*:577

Citrovorum factor (NSC–3590)
absorption of, from a "mouthwash," in man, *59*:575
assay for, in the presence of methotrexate, *59*:935
rescue in the treatment of metastatic bone tumors, *58*:275
toxicity of 24-hour infusions of methotrexate and protection by, in patients with epidermoid carcinoma, *51*:305

Clinical studies: combination of agents
actinomycin D
plus vincristine and cyclophosphamide for embryonal rhabdomyosarcoma, *58*:281
plus vincristine and cyclophosphamide for malignant solid tumors in children, *52*:489

adriamycin
plus bleomycin in adult malignancies, *57*:413
plus CCNU in the treatment of solid tumors, *57*:437
plus cyclophosphamide and vincristine in the treatment of metastatic neuroblastoma, *56*:365
plus cyclophosphamide: a phase I and II evaluation, *58*:919
plus DTIC and vincristine in the treatment of metastatic sarcoma, *58*:265
plus DTIC, central nervous system complications after, *58*:753
plus methotrexate, cyclophosphamide, and 5-FU for adult solid tumors, *58*:943
plus prednisone in metastatic mammary carcinoma, *58*:251
plus various agents in the treatment of various tumors, *58*:49
plus vincristine in metastatic mammary carcinoma, *58*:251
allopurinol plus 6–mercaptopurine during remission of acute leukemia in children, *53*:53
L-asparaginase
plus azaserine in acute lymphatic leukemia, *54*:47
plus cytosine arabinoside in advanced acute lymphocytic leukemia, *56*:363
plus prednisone as a cause of ketotic hyperglycemia, *56*:781
5–azacytidine followed by cyclophosphamide in the treatment of breast cancer, *58*:677
azaserine
plus L-asparaginase in acute lymphatic leukemia, *54*:47
plus 6–thioguanine for multiple myeloma, *51*:234
plus 6–thioguanine for terminal chronic myelocytic leukemia, *58*:233
azotomycin plus 5-FU in colon carcinomas, *54*:109
BCNU
plus cyclophosphamide in bronchogenic carcinoma, *58*:883
plus cyclophosphamide in patients with inoperable or disseminated lung cancer, *56*:401
plus cytosine arabinoside and prednisone for terminal chronic myelocytic leukemia, *58*:233
plus cytosine arabinoside for advanced solid tumors, *56*:53
plus cytosine arabinoside in the treatment of advanced solid tumors, *56*:751
plus cytosine arabinoside in the treatment of cancer, *54*:347
plus 5-FU, DTIC, and vincristine in the treatment of solid tumors, *56*:107
plus 5-FU for disseminated gastrointestinal cancer, *56*:653
plus fluoxymesterone in the treatment of solid tumors, *57*:225
plus postoperative irradiation in malignant gliomas, *58*:841
plus vincristine in disseminated gastrointestinal cancer and other neoplasms, *58*:947
bleomycin
plus adriamycin in adult malignancies, *57*:413
plus dibromodulcitol, effects on squamous cell carcinoma in man, *56*:625
plus vincristine in patients with lung cancer and other malignant tumors, *57*:219
plus vinblastine therapy for disseminated testicular tumors, *58*:213
CCNU
followed by cyclophosphamide in the treatment of breast cancer, *58*:677
plus adriamycin in the treatment of solid tumors, *57*:437
chemotherapy as adjuvant in cancer treatment, *50*:1
chemotherapy following radiotherapy or surgery (Scandinavian Adjuvant Chemotherapy Study Group), *55*:561
cyclophosphamide
after 5–azacytidine or CCNU in the treatment of breast cancer, *58*:677
after surgery in the treatment of stomach and bronchial carcinoma, *56*:35
plus adriamycin and vincristine in the treatment of metastatic neuroblastoma, *56*:365
plus adriamycin: a phase I and II evaluation, *58*:919
plus BCNU in bronchogenic carcinoma, *58*:883
plus BCNU in patients with inoperable or disseminated lung cancer, *56*:401
plus cytosine arabinoside in acute leukemia of children, *53*:299
plus cytosine arabinoside, therapy for acute leukemia, *54*:255
plus DTIC and vincristine in the treatment of metastatic malignant melanoma, *56*:357
plus 5-FU and vincristine: vincristine neuropathy, *58*:413
plus 5-FU, methotrexate, vincristine, and prednisone for disseminated adenocarcinoma, *56*:761
plus methotrexate, adriamycin, and 5-FU for adult solid tumors, *58*:943
plus methotrexate in malignant carcinoid, *51*:239
plus methotrexate in the treatment of cervical carcinoma, *53*:255
plus methotrexate, low dosage, for solid tumors, *54*:41
plus nandrolone phenylpropionate in advanced malignancies, *58*:867
plus radiation therapy in inoperable bronchogenic carcinoma, *51*:189
plus surgery, radiotherapy, vincristine, and daunorubicin for patients with disseminated neuroblastoma, *56*:499
plus vinblastine, short-term sequential therapy with, in Hodgkin's disease, *55*:607
plus vincristine and actinomycin D for embryonal rhabdomyosarcoma, *58*:281
plus vincristine and 5-FU in the treatment of solid tumors, *52*:593
plus vincristine, cytosine arabinoside, and prednisone for acute leukemia in adults, *56*:543
plus vincristine for generalized malignant schwannoma, *54*:65
plus vincristine in a cyclic program, in the treatment of neuroblastoma in children, *51*:411

plus vincristine in neuroblastoma, *58*:683
cytosine arabinoside
plus L-asparaginase in advanced acute lymphocytic leukemia, *56*:363
plus BCNU and prednisone for terminal chronic myelocytic leukemia, *58*:233
plus BCNU for advanced solid tumors, *56*:53
plus BCNU in the treatment of cancer, *54*:347
plus cyclophosphamide in acute leukemia of children, *53*:299
plus cyclophosphamide, therapy for acute leukemia, *54*:255
plus cyclophosphamide, vincristine, and prednisone for acute leukemia in adults, *56*:543
plus daunorubicin, for acute nonlymphocytic leukemia, *57*:485
plus mitomycin C and 5-FU for advanced cancer, *56*:373
plus vincristine and prednisone for acute leukemia in adults, *52*:305
daunorubicin
plus cytosine arabinoside, for acute nonlymphocytic leukemia, *57*:485
plus prednisone or vincristine and prednisone in advanced acute childhood lymphocytic leukemia, *56*:729
plus surgery, radiotherapy, vincristine, and cyclophosphamide for patients with disseminated neuroblastoma, *56*:499
plus vincristine and prednisone for remission induction of childhood acute lymphocytic leukemia, *55*:79
dibromodulcitol, plus bleomycin, effect on squamous cell carcinoma in man, *56*:625
cis-dichlorodiammineplatinum(II), plus various agents in the treatment of cancer, *58*:618
DTIC
plus adriamycin and vincristine in the treatment of metastatic sarcoma, *58*:265
plus adriamycin, central nervous system complications after, *58*:753
plus cyclophosphamide and vincristine in the treatment of metastatic malignant melanoma, *56*:357
plus 5-FU, vincristine, and BCNU in the treatment of solid tumors, *56*:107
emetine plus various agents in the treatment of cancer, *58*:618
estrogens plus orchiectomy for prostatic cancer, *58*:845
experimental approaches to cancer chemotherapy involving metabolites plus antimetabolites, *58*:471
five-drug therapy for advanced breast cancer, *55*:183
fluorometholone, plus 5-FU in advanced gastrointestinal cancer, *51*:77
5-FU
plus azotomycin in colon carcinomas, *54*:109
plus BCNU for disseminated gastrointestinal cancer, *56*:653
plus cyclophosphamide and vincristine in the treatment of solid tumors, *52*:593
plus cyclophosphamide and vincristine: vincristine neuropathy, *58*:413
plus DTIC, vincristine, and BCNU in the treatment of solid tumors, *56*:107
plus fluorometholone in advanced gastrointestinal cancer, *51*:77
plus methotrexate, adriamycin, and cyclophosphamide for advanced solid tumors, *58*:943
plus methotrexate, vincristine, cyclophosphamide, and prednisone for disseminated adenocarcinoma, *56*:761
plus mitomycin C and cytosine arabinoside for advanced cancer, *56*:373
plus oxygen for large bowel carcinoma, *58*:951
plus procarbazine in advanced carcinoma of the lung, *54*:369
plus radiation therapy: an additive effect in bronchogenic carcinoma, *55*:253
plus radiation therapy in bronchogenic carcinoma, *52*:263
plus radiation therapy in inoperable bronchogenic carcinoma, *51*:189
plus various agents given concomitantly in gastrointestinal cancer, *56*:245
plus various agents in the treatment of patients with advanced cancer, *52*:597
fluoxymesterone plus BCNU in the treatment of solid tumors, *57*:225
heparin plus various agents in the treatment of carcinoma of the lung, *56*:783
hexamethylmelamine plus methotrexate in the treatment of carcinoma of the lung, *55*:299
historical controls reincarnated: an examination of techniques for clinical therapeutic research, *58*:623
hydroxyurea
plus irradiation for cervical carcinoma, *52*:601
plus prednisone in the treatment of acute myelocytic leukemia, *55*:199
immunotherapy for leukemia: quantitative aspects and adjuvant relationships to chemotherapy, *53*:3
ineffective single agents used in, *58*:618, *59*:259
initial pharmacologic studies of three types of, *50*:259
in the treatment of nonresectable cancer of the lung, *56*:359
5-iododeoxyuridine
plus radiation therapy in bronchogenic carcinoma, *52*:263
plus radiation therapy in inoperable bronchogenic carcinoma, *51*:189
leucovorin protection plus methotrexate in patients with epidermoid carcinomas, *51*:305
6-mercaptopurine
plus allopurinol during remission of acute leukemia in children, *53*:53
plus methotrexate given iv to adults with acute leukemia, *56*:535
plus 6-methylmercaptopurine ribonucleoside in neuroblastoma, *58*:683
plus 6-methylmercaptopurine riboside in patients with acute leukemia and metastatic cancer, *52*:305
methodologic aspects of cancer chemotherapy after radical surgery, *58*:129
methotrexate
plus adriamycin, cyclophosphamide, and 5-FU for adult solid tumors, *58*:943

plus BCNU in the treatment of advanced solid tumors, *56*:751
plus cyclophosphamide in malignant carcinoid, *51*:239
plus cyclophosphamide in the treatment of cervical carcinoma, *53*:255
plus cyclophosphamide, low dosage, for solid tumors, *54*:41
plus 5-FU, vincristine, cyclophosphamide, and prednisone for disseminated carcinoma, *56*:761
plus hexamethylmelamine in the treatment of carcinoma of the lung, *55*:299
plus 6-mercaptopurine given iv to adults with acute leukemia, *56*:535
plus protection by citrovorum factor in patients with epidermoid carcinomas, *51*:305
plus radiation therapy, treatment of advanced carcinoma of head and neck with, *56*:745
6-methylmercaptopurine ribonucleoside
plus 6-mercaptopurine in neuroblastoma, *58*:683
plus 6-mercaptopurine in patients with acute leukemia and metastatic cancer, *52*:305
mitomycin C
plus 5-FU and cytosine arabinoside for advanced cancer, *56*:373
plus phenylalanine mustard and vincristine in the treatment of osteogenic sarcoma, *55*:189
multiple-drug therapy for malignant solid tumors in adults, *56*:373
nandrolone phenylpropionate plus cyclophosphamide in advanced malignancies, *58*:867
nitromin after surgery in the treatment of stomach and bronchial carcinoma, *56*:35
oxygen plus 5-FU for large bowel carcinoma, *58*:951
phenylalanine mustard plus mitomycin C and vincristine in the treatment of osteogenic sarcoma, *55*:189
postoperative irradiation alone or combined with BCNU in malignant gliomas, *58*:841
prednisone
plus adriamycin in metastatic mammary carcinoma, *58*:251
plus L-asparaginase as a cause of ketotic hyperglycemia, *56*:781
plus BCNU and cytosine arabinoside for terminal chronic myelocytic leukemia, *58*:233
plus cyclophosphamide, vincristine, and cytosine arabinoside for acute leukemia in adults, *56*:543
plus daunorubicin and vincristine for remission induction of childhood acute lymphocytic leukemia, *55*:79
plus daunorubicin or daunorubicin and vincristine in advanced acute childhood lymphocytic leukemia, *56*:729
plus 5-FU, methotrexate, vincristine, and cyclophosphamide for disseminated adenocarcinoma, *56*:761
plus hydroxyurea in the treatment of acute myelocytic leukemia, *55*:199
plus various agents in leukemia and lymphoma, *58*:521
plus vincristine and cytosine arabinoside for acute leukemia in adults, *52*:305
plus vincristine in children with acute leukemia, *54*:293
plus vincristine, remission induction in childhood leukemia with second course, *54*:113
procarbazine plus 5-FU in advanced carcinoma of the lung, *54*:369
pulmonary cysts—a complication in, for Wilms' tumor, *50*:319
radiation therapy
combined with other agents: relevance of cell population kinetics and pharmacodynamics, *53*:313
plus chemotherapy in inoperable bronchogenic carcinoma, *51*:189
plus 5-FU: an additive effect in bronchogenic carcinoma, *55*:253
plus methotrexate, treatment of advanced carcinoma of the head and neck, *56*:745
plus surgery and chemotherapy for patients with disseminated neuroblastoma, *56*:499
with adjuvant chemotherapy, increased clinically symptomatic pulmonary reactions, *58*:705
should ineffective agents be used in?, *58*:127
spontaneous murine mammary adenocarcinoma: model system for evaluation of, *55*:239
surgery
plus chemotherapy in patients with large bowel carcinoma, *56*:551
plus nitromin and cyclophosphamide in the treatment of stomach and bronchial carcinoma, *56*:35
plus radiation therapy and chemotherapy for patients with disseminated neuroblastoma, *56*:499
plus radiation therapy or chemotherapy in breast cancer, *51*:167
synergistic interaction of anticancer agents: a cellular perspective, *59*:895
6-thioguanine
plus azaserine for multiple myeloma, *51*:234
plus azaserine for terminal chronic myelocytic leukemia, *58*:233
thiopurines after prednisone in the treatment of acute childhood leukemia, *52*:321
treatment of metastatic carcinoma of the female breast with combination of hormones and other chemotherapy, *52*:743
uracil mustard plus various agents in uncommon malignant neoplasms in children, *52*:441
using agents with limited effectiveness, *59*:457
various agents in the treatment of gynecologic sarcomas, *51*:507
vinblastine
plus bleomycin therapy for disseminated testicular tumors, *58*:213
plus vincristine as therapy for lymphomas, sarcomas, and other neoplasms, *57*:481
plus vincristine, weekly doses of, in malignant lymphoma and other neoplasms, *57*:477
vincristine
in repeated courses plus various other agents, response of acute leukemia in children, *51*:465
plus actinomycin D and cyclophosphamide for embryonal rhabdomyosarcoma, *58*:281
plus actinomycin D and cyclophosphamide for malignant solid tumors in children, *52*:489

plus adriamycin and cyclophosphamide in the treatment of metastatic neuroblastoma, *58*:365
plus adriamycin in metastatic mammary carcinoma, *58*:251
plus BCNU in disseminated gastrointestinal cancer and other neoplasms, *58*:947
plus bleomycin in patients with lung cancer and other malignant tumors, *57*:219
plus cyclophosphamide and 5-FU in the treatment of solid tumors, *52*:593
plus cyclophosphamide and 5-FU: vincristine neuropathy, *58*:413
plus cyclophosphamide, cytosine arabinoside, and prednisone for acute leukemia in adults, *56*:543
plus cyclophosphamide for generalized malignant schwannoma, *54*:65
plus cyclophosphamide in a cyclic program in the treatment of neuroblastoma in children, *51*:411
plus cyclophosphamide in neuroblastoma, *58*:683
plus daunorubicin and prednisone for remission induction of childhood acute lymphocytic leukemia, *55*:79
plus daunorubicin and prednisone in advanced acute childhood lymphocytic leukemia, *56*:729
plus DTIC and adriamycin in the treatment of metastatic sarcoma, *58*:265
plus DTIC and cyclophosphamide in the treatment of metastatic malignant melanoma, *56*:357
plus 5-FU, DTIC, and BCNU in the treatment of solid tumors, *56*:107
plus 5-FU, methotrexate, cyclophosphamide, and prednisone for disseminated carcinoma, *56*:761
plus mitomycin C and phenylalanine mustard in the treatment of osteogenic sarcoma, *55*:189
plus other agents in central nervous system and other malignant diseases, *52*:733
plus prednisone and cytosine arabinoside for acute leukemia in adults, *52*:305
plus prednisone in children with acute leukemia, *54*:293
plus prednisone, remission induction in childhood leukemia with second course, *54*:113
plus prednisone therapy for acute leukemia in children, *52*:477
plus surgery, radiotherapy, cyclophosphamide, and daunorubicin for patients with disseminated neuroblastoma, *56*:499
plus various agents causing orthostatic hypotension, *58*:927
plus various agents as therapy for Wilms' tumor, *52*:481
plus vinblastine as therapy for lymphomas, sarcomas, and other neoplasms, *57*:481
plus vinblastine, weekly doses of, in malignant lymphoma and other neoplasms, *57*:477
Clinical studies: single agents
A–649 in the treatment of advanced cancer, *53*:71
A–6413, preliminary clinical trial of, *50*:667
1-acetyl-2-picolinoylhydrazine
clinical pharmacologic study of, *53*:131
in the treatment of advanced cancer, *53*:291
in the treatment of carcinoma of the lung, *54*:243
actinomycin D
in the treatment of acute leukemia in children, *57*:335
in the treatment of various tumors, *58*:49
treatment of metastatic Ewing's sarcoma with, *54*:103
adjuvant temperature effects in cancer chemotherapy, *57*:373
adriamycin
compared with daunorubicin in the treatment of late-stage childhood solid tumors, *58*:671
in patients with disseminated breast cancer, *58*:877
in the treatment of acute myelocytic leukemia, *56*:237
on the reported lack of effectiveness of, on solid tumors, *56*:431
pharmacokinetics of, in patients with sarcomas, *58*:271
treatment of Ewing's sarcoma with, *56*:635
alanine mustard, phase II study of, *54*:361
allopurinol
efficacy and lack of toxicity of, given iv, *54*:125
in pediatric neoplasia, *58*:737
1-aminocyclopentanecarboxylic acid, in patients with cancer, *54*:237
6-aminonicotinamide, evaluation of, in the treatment of metastatic hypernephroma, *54*:175
ammonium, trimethylpurin-6-yl-, chloride
in advanced cancer, *52*:417
in the treatment of malignant disease, with special emphasis on cancer of the urinary bladder, *54*:181
L-asparaginase
in the treatment of adult leukemia, *55*:269
pharmacologic studies in man with crystallized, *56*:611
treatment in various cancers, *52*:617
5-azacytidine
compared with CCNU in the treatment of breast cancer, *58*:677
in patients with advanced cancer, *56*:405
in patients with solid tumors, *56*:413
in the treatment of acute leukemia, *57*:319
in the treatment of advanced solid tumors, *58*:217
phase I study of, *58*:899
phase II study of, in advanced gastrointestinal cancer, *56*:649
8-azaguanine, intrathecal perfusion therapy for patients, *50*:283
6-azauridine
chemotherapy for patients with leukemia, *53*:203
in solid tumors, *53*:79
azotomycin
biologic fate in leukemia, *55*:47
treatment in solid tumors, *52*:611
BCNU
in patients with inoperable or disseminated lung cancer, *56*:401
in patients with solid tumors, *56*:787
in the management of patients with advanced breast cancer, *56*:93
in the study of bronchogenic carcinoma, *56*:259
in the treatment of advanced Hodgkin's disease, lymphosarcoma, and reticulum cell sarcoma, *58*:383

in the treatment of advanced solid tumors, *56*:751
in the treatment of brain tumors, *54*:273
in the treatment of bronchogenic carcinoma, *56*:739
in the treatment of Hodgkin's disease and other cancers, *55*:599
in the treatment of Kaposi's sarcoma, *57*:325
in the treatment of malignant brain tumors, *54*:263
response to advanced, using two dosage regimens, *57*:231
toxicity study of, given orally, *58*:407
BIC
given iv, *56*:387
given orally in the treatment of advanced cancer, *55*:159
in the treatment of metastatic malignant melanoma, *56*:671
phase II study of, in advanced gastrointestinal cancer, *56*:267
4,4'biphenylsulfonic acid compounded with 3,3'-(methylamino)di-1-propanol, dimethanesulfonate (ester) in the treatment of malignant lymphoma, *57*:159
3-[bis(2-chloroethyl)amino]-4-methylbenzoic acid, cytogenetic effects of, in human peripheral leukocytes, *57*:29
bleomycin
following Indium 111-labeled tumor scanning to predict response to treatment, *58*:733
in the treatment of advanced epidermoid carcinoma of the uterine cervix, *57*:429
in the treatment of advanced squamous cell carcinoma of the gastrointestinal tract, *57*:493
in the treatment of Kaposi's sarcoma, *57*:325
phase I study, *56*:197
phase II study of, therapy for large bowel cancer, *56*:207
pulmonary toxicity of, *56*:343
busulfan in advanced carcinoma of the prostate, *51*:295
1,3-butanediol, cyclic sulfite, effect of, on lactate dehydrogenase, *50*:85
butocin in patients with generalized carcinoma of the breast, *57*:311
butyraldehyde, 3-ethoxy-2-oxo-, bis(thiosemicarbazone) in advanced cancer, *51*:171
calusterone compared with fluoxymesterone in advanced breast cancer, *58*:939
camptothecin
in advanced cancer, *54*:461
in the treatment of advanced gastrointestinal cancer, *56*:94
in the treatment of malignant melanoma, *56*:103
phase I clinical trials of weekly and daily treatment with, *56*:515
plasma levels in the treatment of advanced cancer, *56*:573
renal clearance of: effect of urine volume, *57*:175
carbazilquinone treatment in solid tumors, *57*:447
carbestrol, phase II study of, in patients with solid tumors, *56*:641
CCNU
compared with 5-azacytidine in the treatment of cyclophosphamide, *58*:677
compared with methyl-CCNU in advanced bronchogenic carcinoma, *58*:913
in the treatment of advanced gastrointestinal cancer, *58*:667
in the treatment of advanced neoplastic disease, *57*:201
in the treatment of brain tumor, phase II study of, *56*:421
in the treatment of malignant brain tumors, *55*:99
treatment in advanced nonhematologic cancer, *58*:421
chlorambucil treatment in 374 patients with advanced cancer, *52*:661
chlormadinone acetate in the treatment of carcinoma of the prostate, *51*:41
chromomycin A_3 in the treatment of advanced cancer, *57*:341
clometherone therapy for metastatic breast carcinoma in women, *50*:327
cyclophosphamide
compared with 6-mercaptopurine as therapy for acute leukemia in children, *51*:381
in neuroblastoma, *58*:683
in patients with inoperable or disseminated lung cancer, *56*:401
in the treatment of acute leukemia in children, *51*:389
in the treatment of Burkitt's lymphoma, *51*:397
in the treatment of children with malignant neoplasms, *51*:403
in the treatment of metastatic malignant melanoma, *54*:365
in the treatment of metastatic testicular neoplasms, *58*:709
in the treatment of multiple myeloma, *56*:563
in the treatment of 127 patients with malignant lymphoma, *50*:265
in the treatment of Wilms' tumor and rhabdomyosarcoma, *51*:407
therapy for children with acute leukemia, *58*:417
therapy for children with generalized lymphoma and Hodgkin's disease, *51*:393
therapy for children with neuroblastoma, *51*:399
urinary excretion of, and its metabolites, *51*:343
cyproterone acetate in the treatment of carcinoma of the prostate, *51*:41
cytosine arabinoside
given sc to patients with cancer, *53*:153
in acute leukemia in children, *50*:287
in the treatment of epidermoid carcinomas of the head and neck, *55*:193
pharmacologic studies of tritiated, in children, *54*:35
plasma half-life in patients treated for acute myeloblastic leukemia, *55*:291
prediction of the response of patients with acute nonlymphocytic leukemia to, *56*:527
therapy for acute leukemia in adults, *53*:59
daunorubicin
compared with adriamycin in the treatment of late-stage childhood solid tumors, *58*:671
in advanced childhood leukemia, *58*:661
in advanced childhood lymphocytic leukemia, *56*:729

in the treatment of advanced acute myelogenous leukemia, *56*:755
in the treatment of metastatic neuroblastoma, *54*:283
on the reported lack of effectiveness of, on solid tumors, *56*:431
6-dehydro-6,17α-dimethylprogesterone for the treatment of metastatic and recurrent ovarian carcinoma, *57*:241
Deluteval 2x in the treatment of metastatic breast cancer, *54*:249
2′-deoxy-5-(trifluoromethyl)uridine, phase I and II studies of, *55*:205
dibromodulcitol
clinical and pharmacologic experience with, *53*:377
in the treatment of advanced tumors, *55*:61
in the treatment of patients with advanced cancer, *55*:583
in the treatment of solid tumors, *55*:567
phase II study of, *58*:653
dibromomannitol
in busulfan-treated patients with refractory chronic myelocytic leukemia and blastic transformation, *58*:223
in patients with chronic myelogenous leukemia, *51*:91
cis-dichlorodiammineplatinum(II)
clinical evaluation of toxic effects of, *57*:465
effects of, on hearing in man, *58*:867
in advanced carcinoma of the large bowel, *57*:357
in solid tumors, *57*:459
in the treatment of advanced unresectable cancer, *57*:191
dichloromethotrexate
in the treatment of liver carcinoma, *56*:249
in the treatment of lung cancer, *57*:79
dihydroxybusulfan in the treatment of solid tumors, *52*:603
dimethanesulfonate, effect of on chronic myelogenous leukemia, *56*:47
2-(dimethylamino)-3′,4′-dihydroxyacetophenone hydrochloride, in solid tumors, *52*:297
1,1-diphenyl-2-propynyl cyclohexanecarbamate, in advanced tumors, *54*:131,187
dromostanolone propionate in the treatment of breast carcinoma, *56*:89
DTIC
effective treatment of Kaposi's sarcoma with, *57*:65
given iv in the treatment of malignant melanoma, *55*:143
intermittent treatment of metastatic malignant melanoma with high-dose, *55*:175
in the treatment of advanced lymphocytic leukemia in children, *56*:523
in the treatment of carcinoma of the lung, *55*:83
in the treatment of disseminated malignant melanoma, *56*:369
in the treatment of disseminated neoplasms, *54*:119
in the treatment of gastrointestinal carcinoma, *54*:471
in the treatment of lymphoma, *56*:667
in the treatment of malignant tumors, *55*:281
treatment in patients with disseminated melanoma, *57*:83
effect of patient selection, in phase II chemotherapy trials in gastrointestinal cancer, *58*:257
emetine
in the treatment of advanced gastrointestinal cancer, *58*:229
in the treatment of solid tumors, *57*:423
estradiol undecylate, effect of massive doses in advanced breast cancer, *51*:491
evaluation of chemotherapy in children with metastatic Ewing's sarcoma and osteogenic sarcoma, *55*:67
experimental screening procedures and clinical predictability value (review), *50*:173
fluorinated pyrimidines, in the treatment of carcinoma of the rectum compared with carcinoma of the colon, *53*:283
5-fluorodeoxyuridine
6-hour iv infusion of, toxic effects and response rate, *51*:81
in the treatment of advanced cancer, *51*:85
fluorometholone
in acute leukemia in children, *50*:339
in advanced gastrointestinal cancer, *51*:77
phase II evaluation of, *51*:525
5-FU
comparison of monthly courses versus weekly doses, *53*:243
effects in 389 patients with cancer, *52*:641
given by the multiple daily dose method in disseminated breast cancer, *51*:483, *57*:59
in advanced gastrointestinal cancer, *51*:77
in colon tumor, using phosphoribosyl transferase as an index of dosage, *58*:909
in disseminated adenocarcinoma, *58*:723
in glucose and saline: therapeutic effect and toxicity, *50*:683
intermittent intra-arterial infusion in outpatients, *50*:331
in the treatment of acute leukemia in children, *57*:335
in the treatment of colorectal carcinoma, *56*:563
in the treatment of patients with advanced cancer, *52*:597
toxicity and chemotherapy, *58*:777
fluoxymesterone compared with calusterone in advanced breast cancer, *58*:939
guanazole in the treatment of childhood leukemia, *58*:715
hadacidin at three fractionated dose levels, *52*:425
heparin in the treatment of carcinoma of the lung, *56*:783
hexamethylmelamine
clinical evaluation of, *57*:51
for small cell carcinoma of the lung, *58*:371
in the treatment of advanced cancer, *56*:505
in the treatment of carcinoma of the cervix, *57*:497
hexestrol treatment in various cancers, *52*:751
historical controls reincarnated: an examination of techniques for clinical therapeutic research, *58*:623
5-hydroxypicolinaldehyde thiosemicarbazone, clinical trials of, *58*:207
hydroxyprogesterone caproate in the treatment of carcinoma of the prostate, *51*:41

hydroxyurea
dose-schedule studies with, in malignant melanoma, *55*:277
given intermittently, treatment of nonresectable cancer of the lung with, *55*:87
high-dose intermittent therapy of solid tumors with, *54*:191
intermittent therapy in malignant diseases, *53*:385
in the treatment of acute myelocytic leukemia, *55*:199
in the treatment of disseminated malignant melanoma, *56*:369
in the treatment of nonresectable cancer of the lung, *52*:271
phase II study of, in malignant melanoma, *51*:503
single reversal trial of, in 91 patients with advanced cancer, *54*:53
studies on the absorption, distribution, and excretion of, *55*:167
N-hydroxyurethan
in the treatment of advanced cancer, *52*:635
in the treatment of solid tumors, *52*:635
ICRF–159
in the treatment of human solid tumors, *57*:185
phase I clinical trial of, *58*:393
3,3′-iminodi-1-propanol, dimethanesulfonate (ester), *p*-toluenesulfonate
in the treatment of malignant lymphoma, *57*:159
treatment of chronic myelogenous leukemia with, given orally, *56*:335
in the treatment of nonresectable cancer of the lung, *58*:359
interferon, induction and host resistance in malignancy, *58*:571
5-iododeoxyuridine given intraventricularly in the treatment of progressive multifocal leukoencephalopathy, *57*:73
isophosphamide
gas chromatographic method for the determination of plasma, *56*:721
in advanced malignancies, *58*:889
in patients with advanced breast cancer, *58*:861
melphalan
administration in osteogenic sarcoma: an evaluation of dosage schedules, *55*:151
in the treatment of advanced breast cancer, *50*:271
in the treatment of disseminated malignant melanoma, *56*:369
in the treatment of multiple myeloma, *56*:563
6-mercaptopurine
compared with cyclophosphamide as therapy for acute leukemia in children, *51*:381
for terminal chronic myelocytic leukemia, *58*:233
given intermittently in high doses, *54*:31
in the treatment of advanced cancer, *51*:277
treatment in 290 patients with advanced cancer, *52*:655
mechlorethamine in the treatment of fever of Hodgkin's disease, *53*:127
methodological aspects of cancer chemotherapy after radical surgery, *58*:129
methotrexate
in squamous cell carcinoma of the head and neck, *51*:69
intermittent parenteral therapy for carcinoma of the lung, *51*:475
interspecies correlation of plasma concentration, *54*:95
in the treatment of advanced epidermoid carcinoma of the uterine cervix, *57*:429
intrathecal therapy for brain tumors in children, *52*:257
parenteral, in malignant carcinoid, *51*:239
phase II study in solid tumors, *51*:471
toxicity of 24-hour infusion of, in patients with epidermoid carcinomas, *51*:305
with citrovorum factor rescue in the treatment of metastatic bone tumors, *58*:275
methyl-CCNU
compared with CCNU in advanced bronchogenic carcinoma, *58*:913
in the treatment of lung cancer, *57*:419
methyl-GAG
administered im in advanced cancer, *58*:689
in the treatment of esophageal cancer, *55*:209
3′3′-(methylimino)di-1-propanol dimethanesulfonate hydrochloride, effect of, on chronic myelogenous leukemia, *56*:47
6-methylmercaptopurine riboside in acute leukemia, *51*:535
methyl methanesulfonate, phase I study, *50*:675
1-methyl-1-nitrosourea, antitumor activity of, *58*:135
7α-methyl-19-nortestosterone, preliminary dose-response studies of, *50*:335
6α-methylpregn-4-ene-3,11,20-trione
in the treatment of solid tumors, *55*:265
phase I clinical study of, *50*:671
methyltrienolone in advanced breast cancer, *54*:453
meturedepa treatment in 233 patients with advanced cancer, *52*:667
mitomycin C
evaluation of dosage schedule of, in children, *55*:285
intermittent dosage schedule of, in solid tumors, *56*:151
in the treatment of colorectal cancer, *53*:287
in the treatment of metastatic osteogenic sarcoma, *53*:297
in various malignant diseases, *54*:195
treatment of 346 patients with advanced cancer, *52*:675
mycophenolic acid
in advanced cancer, *56*:221
in advanced malignancies, *56*:83
metabolic studies in man with, *56*:229
nonhormonal cancer chemotherapy and the vaginal smear, *51*:231
nordihydroguaiaretic acid in the treatment of malignant melanoma, *53*:147
OK–432 in patients with advanced cancer, *56*:211
phenesterin in the treatment of advanced breast cancer, *55*:259
phosphorodiamidic acid, *N,N*-bis(2-chloroethyl)-, cyclohexylamine salt in advanced cancer, *51*:35

piposulfan
clinical experience with, *52*:275
effect of, on malignant lymphomas and solid tumors, *52*:433
in the treatment of chronic granulocytic leukemia, *53*:121
porfiromycin
in large intermittent doses in advanced cancer, *56*:615
in the treatment of disseminated squamous cancer of the cervix, *53*:305
phase I studies of, *51*:283
phase I trial of, in advanced cancer, *51*:497
prednisone
as a cause of nonketotic hyperglycemia, *56*:781
intermittent high-dose therapy with, for multiple myeloma, *51*:179
problems in evaluating tumor responses in the clinical drug evaluation program, *50*:113
procarbazine
high-dose intermittent iv infusion of, *57*:361
in the treatment of acute leukemia, *57*:371
in the treatment of advanced bronchogenic carcinoma, *53*:135
in the treatment of advanced Hodgkin's disease, *53*:39
in the treatment of multiple myeloma, *54*:245
response of childhood histiocytosis X to, *58*:719
pseudourea in the treatment of metastatic cancer, *55*:91
quantitative comparison of toxicity of anticancer agents in man and various animals, *50*:219
retinoblastoma treated with various agents, *52*:631
sangivamycin in advanced cancer, *51*:197
L-sarcolysin therapy for children with metastatic neuroblastoma, *52*:293
DL-metasarcolysin for advanced carcinoma of the breast, *52*:413
ortho-DL-sarcolysin
for advanced carcinoma of the breast, *52*:413
in the treatment of multiple myeloma, *51*:517
in the treatment of solid tumors, *50*:685
SPG–827 in the treatment of advanced cancer, *50*:565
SPI–77 in the treatment of advanced cancer, *50*:565
streptonigrin in the treatment of advanced gastrointestinal cancer, *51*:73
streptozotocin
glucose tolerance and insulin response before and after treatment with, in patients with cancer, *56*:61
nephrotoxicity of, *54*:457
in the treatment of advanced gastrointestinal cancer, *55*:303
Δ^1-testololactone
for advanced breast cancer, *50*:323
in the treatment of metastatic breast cancer, *54*:249
tilorone, a non-marrow-depressing agent, in the treatment of advanced cancer, *57*:209
tissue-specific chemotherapy, *54*:375
toyocamycin, phase I study of, *52*:301
trimethylcolchicinic acid, methyl ether
in patients with malignant melanoma, *56*:263
in the treatment of advanced cancer, *51*:25
tris(2,2-dimethyl-1-aziridinyl)phosphine oxide in advanced cancer, *56*:393
tryptophan mustard in the treatment of acute leukemia and malignant solid tumors in children, *52*:445
uracil mustard
therapy for children with metastatic neuroblastoma, *52*:287
therapy in uncommon malignant neoplasms in children, *52*:441
various agents in the treatment of gynecologic sarcomas, *51*:507
vinblastine
arterial infusion of, in patients with solid tumors, *50*:573
in the treatment of advanced Hodgkin's disease, *53*:39
in the treatment of bronchogenic carcinoma, *54*:451
vincristine
effectiveness against refractory leukemia in children, *52*:473
effect of, on malignant solid tumors in children, *52*:497
in low doses for malignant disease, *53*:249
in the treatment of children with acute leukemia, *52*:469
response of acute leukemia in children to repeated courses of, *51*:465
therapy for acute leukemia in children, *52*:477
therapy for malignant solid tumors in children, *52*:485
therapy for Wilms' tumor, *52*:481
treatment in tumors of the central nervous system and other malignant diseases, *52*:733
vinleurosine in the treatment of advanced cancer, *50*:95
VM–26
in patients with malignant lymphomas and solid tumors, *56*:71
in the treatment of advanced cancers, *55*:575
VP–16–213
phase I clinical trial of, *56*:769
weekly administration of, *58*:901
what shall we measure on whom? why?, *50*:107
Clometherone, hormonal therapy for metastatic breast carcinoma in women, *50*:327
Colcemid *see* Demecolcine
Colchicine (NSC–757)
activated specifically by PAP, as a potential cytotoxic agent, *59*:233
modification in biochemical pathways produced by, *52*:501
plus deuterium oxide in chemotherapy on transplantable mouse tumors, *50*:641
Colon carcinoma *see* Carcinoma, colon
Colorectal cancer *see* Carcinoma, colorectal
Combination therapy *see* Clinical studies: combination of agents
Compound 593A (NSC–135758), chemotherapeutic effects of, on mouse leukemias and some transplanted animal tumors, *57*:21
Computers
automated response-decisions in cancer chemotherapy trials, *57*:137
electronic, for evaluation of clinical data, man versus machine, *50*:141
electronic, for evaluation of clinical data, man versus man, *50*:151

electronic, for evaluation of clinical data, interpretation of data, *50*:157
models for tumor growth and chemotherapy and its application to L1210 leukemia treated with cytosine arabinoside, *54*:399
Concanavalin A (NSC–143504), molecular pharmacology of, *58*:491
Connective tissue cancer *see* Carcinoma in man, connective tissue
Corticosteroids, structure-toxicity relations of some, *51*:225
Corynebacterium parvum, phase I study in patients with various solid tumors, *59*:1139
Cross resistance, between vinca alkaloids and anthracyclines in Ehrlich ascites tumor in vitro, *56*:701
Cyclocytidine (NSC–145668)
distribution of, compared with cytosine arabinoside in mice, *59*:501
evaluation of sialogogic action of, *59*:1019
phase I evaluation of, in the treatment of acute leukemia and solid tumors, *59*:389
***O*-2,2′-Cyclocytidine, monoacetate** *see* Cyclocytidine
Cyclohexylamine salt of *N,N*-bis(2-chloroethyl)phosphorodiamidic acid *see* Phosphorodiamidic acid, *N,N*-bis(2-chloroethyl)-, cyclohexylamine salt
Cyclohexylisocyanate (NSC–87419), effects on progression of L1210 cells through the cell cycle, *55*:215
Cycloleucine (NSC–1026)
immunodepressive activity of, in mice, *56*:579
phase II study of, in patients with cancer, *54*:237
Cyclophosphamide (NSC–26271)
after 5-azacytidine or CCNU in patients with breast cancer, *58*:677
after surgery in the treatment of stomach and bronchial carcinoma, *56*:35
alone or combined with BCNU in patients with inoperable or disseminated lung cancer, *56*:401
alone or combined with cytosine arabinoside in the treatment of AKR leukemia, *56*:683
combined with *cis*-dichlorodiammineplatinum(II) in the treatment of human malignancies, *59*:995
alone or combined with vincristine in neuroblastoma, *58*:683
altered sensitivity of hematopoietic stem cells to 5-FU following, *58*:813
animal investigations with (review), *52*:359
combination therapy including vincristine for malignant solid tumors in children, *52*:489
combination therapy with vincristine and 5-FU, *52*:593
combined with cytosine arabinoside and methotrexate in the treatment of advanced breast and lung cancer, *59*:1091
combined with BCNU in the remission maintenance of adult acute nonlymphocytic leukemia, *59*:537
combined with 5-FU with or without vincristine in the treatment of various adenocarcinomas, *59*:425
combined with hormones in the treatment of metastatic carcinoma of the female breast, *52*:743
combined with methotrexate in the treatment of malignant carcinoid, *51*:239
combined with methyl-CCNU and vincristine in the treatment of small cell cancer of the lung in a 3-week schedule, *59*:1127
combined with methyl-CCNU in a comparative study with DTIC plus vincristine in patients with disseminated malignant melanoma, *59*:451
combined with methyl-CCNU in the treatment of advanced gastrointestinal cancer, *59*:1161
combined with prednisone with or without chloroquine in the treatment of multiple myeloma resistant to melphalan, *59*:557
combined with vincristine and actinomycin D with or without radiation therapy in the treatment of childhood rhabdomyosarcoma, *59*:359
compared with dibromodulcitol as remission maintenance therapy in previously treated children with acute lymphocytic or acute undifferentiated leukemia: possible effectiveness in reducing the incidence of central nervous system leukemia, *59*:989
compared with 5-FU in patients with advanced prostatic cancer, *59*:195
compared to 5-FU in the treatment of bronchogenic cancer, *59*:1025
compared with 6-mercaptopurine as therapy for acute leukemia in children, *51*:381
continuing long-term remission after therapy for canine leukemia, *53*:223
continuous and limited courses of, in mice with pulmonary metastasis after surgery, *51*:439
cure of metastatic Lewis lung carcinoma with methyl-CCNU and surgery-chemotherapy, *56*:183
development of immunity to L1210 leukemia in BDF_1 mice and effects of, *50*:55
effect of different doses of, on drug resistance in mice with L1210 leukemia, *56*:473
effect of nandrolone phenylpropionate on the bone marrow suppression caused by, *58*:867
effect of, on NAD glycohydrolase in normal and leukemic mouse tissues, *52*:569
effect of, on 127 patients with malignant lymphoma, *50*:265
effect of, on primary and metastatic plasmacytoma in the hamster, *52*:345
evaluation in the C1300 murine neuroblastoma model, *59*:975
given alone or combined with vincristine and prednisone (COP) in the treatment of diffuse non-Hodgkin's lymphoma, *59*:421
hemorrhagic encephalopathy induced by, in suckling rats, *54*:211
high-dose, in the treatment of metastatic testicular neoplasms, *58*:709
high-dose, in the treatment of recurrent or progressive ovarian adenocarcinoma, *59*:1157
high-dose therapy in childhood acute leukemia, *58*:417
immediate cerebral symptoms during rapid iv administration of, *59*:441
inhibition of antilymphoma allograft response in normal and lethally irradiated mice by, *59*:967
intermittent high-dose treatment of stage III ovarian cancer, *58*:697
in the treatment of acute leukemia in children, *51*:389

in the treatment of children with malignant neoplasms, *51*:403
in the treatment of multiple myeloma, *56*:563
in the treatment of neuroblastoma, *58*:683
kinetic parameters and cell cure in Carcinoma 755, *53*:169
large intermittent iv doses of, in the treatment of metastatic malignant melanoma, *54*:365
L1210 leukemia death in vivo after administration of, *53*:273
low-dosage methotrexate and, for solid tumors, *54*:41
metabolism and antitumor activity of, in animals, *51*:377
metabolism of, *51*:341
new model for studying the effects of, on the growth of the prostate gland in rats, *59*:185
oropharyngeal sensation associated with rapid iv administration of, *56*:779
pharmacologic characterization of, and its metabolites, *51*:315
pharmacologic studies of, and its congener, phosphoramide mustard, *51*:335
plus adriamycin and vincristine in the treatment of metastatic neuroblastoma, *58*:365
plus adriamycin: a phase I and II evaluation, *58*:919
plus BCNU for advanced solid tumors, *56*:53
plus BCNU in bronchogenic carcinoma, *58*:883
plus cytosine arabinoside in acute leukemia of children, *53*:299
plus cytosine arabinoside, therapy of acute leukemia, *54*:255
plus deuterium oxide in chemotherapy on transplantable mouse tumors, *50*:641
plus DTIC and vincristine, treatment of metastatic malignant melanoma with, *56*:357
plus 5-FU and vincristine: vincristine neuropathy, *58*:413
plus 5-FU, compared with adriamycin in the treatment of advanced prostatic cancer, *59*:203
plus 5-FU, methotrexate, vincristine, and prednisone for disseminated adenocarcinoma, *56*:761
plus methotrexate, adriamycin, and 5-FU for adult solid tumors, *58*:943
plus methotrexate in the treatment of cervical carcinoma, *53*:255
plus surgery, radiotherapy, vincristine, and daunorubicin for patients with disseminated neuroblastoma, *56*:499
plus vincristine and actinomycin D for embryonal rhabdomyosarcoma, *58*:281
plus vincristine, cytosine arabinoside, and prednisone: combination for acute leukemia in adults, *56*:543
plus vincristine for generalized malignant schwannoma, *54*:65
plus vincristine in a cyclic program in the treatment of neuroblastoma in children, *51*:411
prevention by, of immunosuppression by BCG, *58*:931
recent biologic and chemical studies, *51*:327
relationship of dose schedules of, after surgery in Lewis lung tumor, *54*:379
response to spontaneous, first passage, and long-term passage lines of AKR leukemia, *53*:345
role of lysosomal labilizers in the treatment of mammary gland carcinomas with, *50*:47
sequential chemotherapy with, and cytosine arabinoside in mice with advanced L1210 leukemia, *53*:265
short-term sequential therapy with vinblastine and, in Hodgkin's disease, *55*:607
standard-dose versus high-dose versus cyclophosphamide plus cytosine arabinoside in the maintenance treatment of childhood acute lymphocytic leukemia, *59*:1097
teratogenic effects of, in the rat, *51*:363
therapy for children with generalized lymphoma and Hodgkin's disease, *51*:393
therapy for children with neuroblastoma, *51*:399
treatment in metastatic retinoblastoma, *52*:631
treatment in Wilms' tumor and rhabdomyosarcoma, *51*:407
treatment of MAC–13 and MAC–15, adenocarcinomas of the colon in mice, *59*:1083
treatment of nonlymphoid solid tumors, *59*:411
urinary excretion of, and its metabolites: evidence for the existence of an "active" cyclic metabolite, *51*:343
used in potential test systems in animals to determine activity against prostatic cancer, *59*:175

Cyproterone acetate (NSC–81430)
effect of, on carcinoma of the prostate, *51*:41
new model for studying the effects of, in the growth of the prostate gland in rats, *59*:185

Cytembena (NSC–104801)
nephrotoxic effects of, in dogs and monkeys, *59*:1071
phase II study of, in advanced colorectal cancer, *59*:581

Cytosine arabinoside (NSC–63878)
analysis of the effects of, on cell cycle kinetics, *59*:847
alone or in combination with cyclophosphamide in the treatment of AKR leukemia, *56*:683
alone or in combination with 6-mercaptopurine, methotrexate, or 5-FU in L1210 mouse leukemia, *51*:435
altered sensitivity of a hamster plasmacytoma to, *54*:337
combined with cyclophosphamide and compared to high-dose cyclophosphamide or standard-dose cyclophosphamide in the maintenance treatment of childhood acute lymphocytic leukemia, *59*:1097
combined with cyclophosphamide and methotrexate in the treatment of advanced breast and lung cancer, *59*:1091
combined with daunorubicin, 6-thioguanine, prednisone, and vincristine in the treatment of adults with acute nonlymphocytic leukemia, *59*:1131
combined with daunorubicin, vincristine, and prednisone in the treatment of advanced adult acute leukemia, *59*:757
disposition of, and its metabolites: a pharmacokinetic simulation, *59*:861
compared with anhydro-ara-C activity in L1210 leukemia, with respect to treatment schedule dependency, *56*:483
computer model for tumor growth and chemotherapy and its application to L1210 leukemia treated with, *54*:399
development of herpes zoster in a patient with acute leukemia after therapy with, *53*:49

differential sensitivities of normal and L1210 leukemia bone marrow colony-forming cells to single- and divided-dose therapy with, *51*:423
disposition of, in solid L1210 leukemia tumor-bearing mice, *57*:275
distribution of, compared with cyclocytidine in mice, *59*:501
effect of different doses of, on drug resistance in mice with L1210 leukemia, *56*:473
improved microbiologic assay for, *54*:393
in acute leukemia in children, *50*:287
influence of mitotic inhibitors on the antileukemic activity of, in mice bearing L1210 leukemia, *55*:547
influence of route of administration on antileukemic activity of, in advanced L1210 leukemia in mice, *52*:399
influence of the stage of advancement of L1210 leukemia in mice on the optimal schedule of treatment of, *56*:327
inhibition of deamination of, by rhodium(II) acetate, *59*:661
inhibition of deamination of, by tetrahydrouridine, *59*:717
in the treatment of epidermoid carcinomas of the head and neck, *55*:193
microbiologic assay for, in biologic materials containing other antitumor or antibacterial drugs, *55*:557
microbiologic assay for, using a mutant of *Streptococcus faecium* var. *durans* resistant to methotrexate and 6-mercaptopurine, *59*:515
pharmacologic studies of tritiated, in children, *54*:35
plasma half-life of, in patients treated for acute myeloblastic leukemia, *55*:291
plus L-asparaginase, effective treatment of advanced acute lymphocytic leukemia, *56*:363
plus BCNU and prednisone in the treatment of terminal chronic myelocytic leukemia, *58*:233
plus BCNU in the treatment of advanced solid tumors, *56*:751
plus BCNU in the treatment of cancer, *55*:347
plus BCNU in the treatment of Sarcoma 180 and L1210 leukemia in vivo, *53*:215
plus cyclophosphamide in acute leukemia of children, *53*:299
plus cyclophosphamide, therapy of acute leukemia, *54*:255
plus cyclophosphamide, vincristine, and prednisone combination for acute leukemia in adults, *56*:543
plus daunorubicin, therapy for acute nonlymphocytic leukemia, *57*:485
plus DTIC in advanced murine L1210 leukemia and enhancement of the combination with sequential doses of methotrexate or BCNU, *57*:291
plus mitomycin C and 5-FU for advanced cancer in man, *56*:373
plus 6-thioguanine in, cytosine arabinoside-sensitive and -resistant P815 mouse neoplasms, *57*:349
plus vincristine and prednisone, therapy for acute leukemia in adults, *52*:305
prediction of the response of patients with acute nonlymphocytic leukemia to, *56*:527
proposed new derivative of, to circumvent resistance, *58*:298
radiosensitization of bacteria by, *51*:229
response in male and female mice with Taper liver tumor, *53*:325
response to spontaneous, first passage, and long passage lines of AKR leukemia, *53*:345
sc administration of, to patients with cancer, *53*:153
scheduling of, to take advantage of its S-phase specificity against leukemia cells, *51*:125
sequential chemotherapy with cyclophosphamide and, in mice with advanced L1210 leukemia, *53*:265
therapy for acute leukemia in adults, *53*:59

D

Daunomycin *see* Daunorubicin
Daunomycin, *N*-(butylcarbamoyl)- (NSC–143496), toxicologic screening in rats, *59*:707
Daunomycin-DNA (NSC–169533), comparison of different formulations of, *59*:260
Daunomycin-semicarbazone (NSC–143114), toxicologic screening in rats, *59*:707
Daunorubicin (NSC–82151)
allergic reaction to, *54*:475
alone or plus prednisone or plus vincristine and prednisone in advanced childhood lymphocytic leukemia, *56*:729
antitumor activity and cardiotoxicity of, another hypothesis, *59*:258
biologic activity of, in microbial systems, *52*:707
compared with adriamycin against mouse mammary carcinoma, *56*:153
compared with adriamycin in the treatment of late-stage childhood solid tumors, *58*:671
comparison of antileukemic effect of adriamycin with, *54*:1
combined with cytosine arabinoside, 6-thioguanine, prednisone, and vincristine in the treatment of adults with acute nonlymphocytic leukemia, *59*:1131
combined with methotrexate in the remission-maintenance treatment of acute lymphocytic leukemia, *59*:395
combined with vincristine, cytosine arabinoside, and prednisone in the treatment of advanced adult acute leukemia, *59*:757
contact dermatitis associated with, *59*:677
cross resistance between vinca alkaloids and anthracyclines in Ehrlich ascites tumor in vivo, *56*:701
cytotoxic, antiviral, and antitumor activity of some derivatives of, *57*:269
development of resistance to, in Ehrlich ascites tumor, *55*:133
distribution of tritiated, in normal rats, *52*:331
DNA complexes of, *59*:260
effectiveness of, against experimental tumors, *50*:659
enhancement of the effectiveness of, combined with adriamycin against early mouse L1210 leukemia with ICRF–159, *59*:689

fluorometric determination of serum levels and urinary excretion of, in mice and rats, *53*:159
high-dose, in the treatment of advanced acute myelogenous leukemia, *56*:755
hypothesis concerning antitumor activity and cardiotoxicity, *58*:293
in advanced childhood leukemia, *58*:661
in the treatment of metastatic neuroblastoma, *54*:283
metabolism of, in vitro and the chemotherapeutic activity of isolated metabolites in vivo, *56*:315
pathologic changes induced by, in the Syrian golden hamster, *54*:15
plus cytosine arabinoside therapy in acute nonlymphocytic leukemia, *57*:485
plus surgery, radiotherapy, vincristine, and cyclophosphamide for patients with disseminated neuroblastoma, *56*:499
plus vincristine and prednisone for remission induction of childhood acute lymphocytic leukemia, *55*:79
reported lack of effectiveness of, on solid tumors, *56*:431
some determinants of the therapeutic efficacy of, *58*:55
tissue distribution and disposition of, in mice: fluorometric and isotopic methods, *54*:89
toxicology screening in rats, *59*:707
Deaza-aminopterin (NSC–529860), dosage schedules in L1210 leukemia and toxicity, *55*:123
6-Dehydro-6,17-α-dimethylprogesterone (NSC–123018), for the treatment of metastatic and recurrent ovarian carcinoma, *57*:241
Deluteval 2x (NSC-77622), comparison with Δ^1-testololactone in the treatment of metastatic breast cancer, *54*:249
Demecolcine (NSC–3096), alone or with mechlorethamine in pretreatment of V × 2 carcinoma undergoing isolation perfusion, *56*:175
4′-Demethylepipodophyllotoxin, 9-(4,6-*O*-ethylidene-β-D-glucopyranoside) *see* VP–16–213
4′-Demethylepipodophyllotoxin, 9-(4,6-*O*-2-thenylidene-β-D-glucopyranoside) *see* VM–26
2′-Deoxy-5-fluorouridine *see* 5-Fluorodeoxyuridine
4-Deoxypyridoxine hydrochloride (NSC–3063), effect of pyridoxal phosphate on toxicity and antitumor activity of, in rats, *50*:313
2′-Deoxy-5-(trifluoromethyl)uridine (NSC–75520), phase I and II studies of, *55*:205
Deuterium oxide, plus chemotherapy on transplantable mouse tumors, *50*:641
2,4-Diamino-quinazoline *see* Methasquin
1,2:5,6-Dianhydrogalactitol (NSC–132313)
pharmacologic and antitumor effects of, *56*:593
survival and phase sensitivity of HeLa cells treated with, *59*:493
***N*-Diazoacetylglycine hydrazide (NSC–58404)**, toxicity of, in animals, *53*:13
6-Diazo-5-oxo-L-norleucine *see* DON
Dibromodulcitol (NSC–104800)
comparative effects of, in the treatment of various cancers, *53*:377
compared with cyclophosphamide as remission maintenance therapy in previously treated children with acute lymphocytic or acute undifferentiated leukemia: possible effectiveness in reducing the incidence of central nervous system leukemia, *59*:989
initial clinical trial with, in patients with advanced cancer, *55*:583
in the treatment of solid tumors, *55*:567
metabolic pathway of, *51*:261
phase I study of, *55*:61
phase II study of, *58*:653
plus bleomycin, effect on squamous cell carcinoma in man, *56*:625
Dibromomannitol (NSC–94100)
clinical study of previously treated patients with chronic myelocytic leukemia and blastic transformation, *58*:223
in patients with chronic myelogenous leukemia, *51*:91
metabolic pathway of, *51*:261
***cis*-Dichlorobiscyclopentylamineplatinum(II)**
antitumor activity and tissue distribution of, in animals, *59*:629
chemistry of, *59*:589
preliminary clinical studies with, *59*:647
***cis*-Dichlorodiammineplatinum(II) (NSC–119875)**
action of, at the cellular level, *59*:665
acute toxicologic and pathologic effects of, in the male rat, *55*:1
alone or combined with various other agents in the treatment of murine L1210 leukemia, *59*:629
antitumor activity of, in various animal tumors, *59*:589
biologic and chemical effects of, on DNA, *59*:643
clinical evaluation of toxic effects of, phase I clinical study, *57*:465
clinical trials of, *57*:191
combined with cyclophosphamide in the treatment of human malignancies, *59*:995
compared to other platinum compounds, activity against experimental animal tumors, *59*:287
effects of, on hearing function in man, *58*:871
effect of, on the allograft reaction in mice, *58*:633
hearing loss and other toxic effects in rhesus monkeys treated with, *59*:467
inhibition of Dunning ascitic leukemia and Walker 256 carcinosarcoma with, *55*:325
phase I study, *57*:459
phase II study of, in advanced carcinoma of the large bowel, *57*:357
tissue analysis, toxicity, and antitumor activity of, in nonleukemic patients, *59*:647
treatment of lymphomas and ovarian, head and neck, and testicular cancers, *59*:621
Dichloromethotrexate (NSC–29630)
comparison of two dose schedules of, in lung cancer, *57*:79
preliminary clinical trials of, in liver carcinoma, *56*:249
Diethylstilbestrol (NSC–3070)
plus 5–FU or alone in the treatment of stage D prostate adenocarcinoma, *59*:243
treatment of metastatic carcinoma of the female breast alone or in combination with other chemotherapy, *52*:743
treatment of prostatic carcinoma, *59*:225
Dihydrofolate reductase, inhibition, structure-activity cor-

relations of anticancer agents: diaminopyrimidines, *N*-acyltriamines, bis-(1-aziridinyl)-phosphinyl carbamates, and aromatic nitrogen mustards, *57*:251
2,3-Dihydro-2-(1-naphthyl)-4(1*H*)-quinazolinone (NSC–145669), antitumor effects of the antispermatogenic agent against L1210 leukemia, *56*:163
Dihydroxybusulfan (NSC–39069), clinical trials with, *52*:603
2,3-Dihydroxypropanal (NSC–67934), indefinite survivors among mice treated with, *52*:687
Dimethanesulfonate (NSC–102627)
effect of, on chronic myelogenous leukemia, *56*:47
treatment of chronic myelogenous leukemia with, given orally, *56*:335
Dimethanesulfonate sugar derivative (NSC–122402), and related compounds, antileukemic action of, in mice, *53*:367
2-(Dimethylamino)-3′,4′-dihydroxyacetophenone hydrochloride (NSC–62512), phase I clinical study of, in solid tumors, *52*:297
5-(3,3-Dimethyl-1-triazeno)imidazole-4-carboxamide *see* DTIC
Diphenamid (NSC–93415), treatment of experimental mammary adenocarcinoma with, *58*:745
1,1-Diphenyl-2-propynyl cyclohexanecarbamate (NSC–112682)
clinical trial of, *54*:187
initial clinical trials with, *54*:131
DNA
binding of actinomycin D analogs in fluorescent binding studies, *58*:35
biologic and chemical effects of *cis*-dichlorodiammine-platinum(II) on, *59*:643
biosynthesis, X-ray sensitization by halopyrimidines (review), *58*:539
effect of mannitol mustard on nuclear, in HeLa and Chinese hamster cells, *53*:115
molecular evidence for viral agents in human cancer and its chemotherapeutic consequences, *58*:595
origins of base specificity in actinomycin and other ligands, *58*:97
radiation repair mechanisms in radiation treatment failures, *58*:527
scheduling of cytosine arabinoside to take advantage of its S-phase specificity against leukemia cells, *51*:125
stereochemistry of actinomycin binding to, *58*:101
DNA polymerase
effect of streptonigrin and analogs on oncornavirus replication and DNA polymerase activity, *57*:305
inhibition of Rauscher leukemia virus and avian myeloblastosis virus, by tilorone and its analogs, *58*:821
DON (NSC–7365), biosynthesis of, from azotomycin in vivo, *55*:47
DPD *see* Diphenamid
Dromostanolone propionate (NSC–12198), clinical experience with, in breast carcinoma, *56*:89
Drug design
quantitative structure-activity relationships of nitrosoureas and triazenoimidazoles in the treatment of L1210 leukemia, *56*:443
strategy of (commentary), *56*:433
Drug resistance
development of, to adriamycin in Ehrlich ascites tumor in vivo, *56*:321
effectiveness of antileukemic agents in mice with an L1210 leukemia variant resistant to BIC, *53*:229
effect of different doses of methotrexate, cytosine arabinoside, and cyclophosphamide on, in mice with L1210 leukemia, *56*:473
failure of combination therapy with *S*-carbamyl-L-cysteine and L-asparaginase for L-asparaginase-resistant mouse lymphoma, *56*:339
interferon: its inducers and aspects of host resistance in malignancy, *58*:571
proposed new derivative of cytosine arabinoside to circumvent resistance, *58*:298
quick reference chart on cross resistance between anticancer agents, *56*:493
Drug schedules
implications of biochemical, cytokinetic, pharmacologic, and toxicologic relationships in the design of optimal, *54*:431
relationship of, to the effectiveness of adjuvant chemotherapy, *54*:379
Drug screening *see also* Tumor systems in animals
cell survival and repair of plateau-phase cultures after chemotherapy—relevance to tumor therapy and to in vitro, of new agents, *57*:473
developing need for perspective in surveys of antitumor test data, *54*:299
management of the National Cancer Institute's drug research program through application of the linear array concept, *54*:303
methods of, in the Soviet Union, *54*:71
procedures, *54*:294
with experimental tumors which metastasize to lymph nodes, *54*:311
DTIC (NSC–45388)
cell-mediated response to a mouse leukemic subline antigenically altered following treatment in vivo, *58*:325
clinical trials of, given iv in the treatment of malignant melanoma in Uganda, *55*:143
clinical trials with, *54*:119
colorimetric determination in blood, *53*:199
combined with adriamycin in the treatment of advanced, childhood, stage IV neuroblastoma, *59*:1015
combined with vincristine in a comparative study with cyclophosphamide plus methyl-CCNU in patients with disseminated malignant melanoma, *59*:451
effective treatment of Kaposi's sarcoma with, *57*:65
effectiveness of antileukemic agents in mice inoculated with L1210 leukemia variants resistant to, *55*:9
evaluation in the C1300 murine neuroblastoma model, *59*:975
intermittent treatment of metastatic malignant melanoma with high-dose, *55*:175
in the treatment of advanced acute lymphocytic leukemia in children, *56*:523
in the treatment of disseminated malignant melanoma, *56*:369
in the treatment of lymphoma, *56*:667
in the treatment of malignant tumors other than melanoma, *55*:281
in the treatment of patients with gastrointestinal carcinoma, *54*:471

kinetics of the effect of, on the reproductive integrity of cultured L1210 leukemia cells, *52*:725
metabolism of, in human and animal tissues, *56*:465
microbiologic assay in mouse tissues, *52*:553
new model for studying the effects of, in the growth of the prostate gland in rats, *59*:185
plus adriamycin and vincristine in the treatment of metastatic sarcoma, *58*:265
plus adriamycin, central nervous system complications after treatment with, *58*:753
plus cyclophosphamide and vincristine, treatment of metastatic malignant melanoma with, *56*:357
plus cytosine arabinoside in advanced L1210 leukemia and enhancement of the combination with sequential doses of methotrexate or BCNU, *57*:291
plus 5–FU, vincristine, and BCNU given concomitantly in the treatment of solid tumors in man, *56*:107
spleen colony studies of L1210 leukemia, sensitivities of L1210 and L1210/6-MP to, *52*:393
stochastic compartmental modeling of the disposition of, *59*:843
study of, in patients with disseminated melanoma, *57*:83
treatment of carcinoma of the lung, *55*:83
treatment of solid tumors in children, *59*:351
used in potential test systems in animals to determine activity against prostatic carcinoma, *59*:175

Dunning ascites tumor *see* Tumor systems in animals, leukemia, Dunning ascites

E

Ehrlich ascites tumor *see* Tumor systems in animals, carcinoma, Ehrlich ascites

Ellipticine (NSC–71795)
and some ellipticine analogs, comparison of the acute hemolytic and cardiovascular actions of, *58*:637
prevention of hemolysis induced by, in rhesus monkeys, *58*:171
strategy in drug design, *56*:433

Emetine (NSC–33669)
phase I–II studies in the treatment of epidermoid bronchogenic cancer, *59*:1171
phase II study of, in the treatment of solid tumors, *57*:423
treatment of advanced gastrointestinal cancer with, *58*:229

Endotoxin (NSC–189681), altered sensitivity of hematopoietic stem cells to 5-FU following, *58*:813

Epidermoid carcinoma *see* Carcinoma in man, squamous cell

Erythropoiesis, effect of testosterone enanthate on, in irradiated mice given marrow transfusions, *52*:627

Esophageal cancer *see* Carcinoma in man, esophageal

Estradiol (NSC–9895), new model for studying the effects of, in the growth of the prostate gland in rats, *59*:185

Estradiol binding protein, estradiol mustard and phenester: possible mediation of action by, *58*:353

Estradiol mustard (NSC–112259)
and its molecular components, treatment in vivo of R3230AC of the rat with, *57*:353
possible mediation of action by estrogen binding protein, *58*:353

Estradiol undecylate, effect of massive doses of, in advanced breast cancer, *51*:491

Estramustine phosphate (NSC–89199)
clinical results with, in far-advanced prostatic carcinoma: comparison of iv and oral preparations, *59*:229
new model for studying the effects of, in the growth of the prostate gland in rats, *59*:185
oral, in the treatment of advanced (stage D) prostatic carcinoma, *59*:219

Estrogens
alone or plus orchiectomy for prostatic cancer, *58*:845
prediction of breast cancer response to, *58*:513

Estrogen-progestin combination *see* Deluteval 2x

3-Ethoxy-2-oxo-butyraldehyde bis(thiosemicarbazone) *see* Butyraldehyde, 3-ethoxy-2-oxo-, bis(thiosemicarbazone)

9-Ethyl-6-mercaptopurine (NSC–14575), for acute leukemia in children, after remission on prednisone, *52*:321

Ewing's sarcoma *see* Sarcoma, Ewing's

F

5-Fluorodeoxyuridine (NSC–27640; 5-FUDR)
chemotherapy of Morris hepatoma 3924A: correlation of size and weight of tumor and preliminary data with, *57*:245
comparative response of carcinoma of the rectum and of the colon to fluorinated pyrimidines, *53*:283
further clinical evaluation, *51*:85
6-hour iv infusions of; toxic effects and response rate, *51*:81

Fluorometholone (NSC–33001)
alone or combined with 5-FU in advanced gastrointestinal cancer, *51*:77
in acute leukemia in children, *50*:339
phase II evaluation of, *51*:525

5-Fluorouracil (NSC–19893; 5-FU)
activity against human tumor xenografts in immune-deprived mice, *58*:645
alone or combined with fluorometholone in advanced gastrointestinal cancer, *51*:77
altered sensitivity of hematopoietic stem cells to, following endotoxin, cyclophosphamide, or irradiation, *58*:813
applied in a mouthwash in the treatment of residual or relapsing cancer of the lip or buccal mucosa, *59*:1052
bronchial artery infusion of, in bronchogenic carcinoma, *52*:263
cardiotoxicity of, in man, *59*:1051
cerebellar ataxia during therapy, *55*:595
clinical pharmacology of oral and iv, in disseminated adenocarcinoma, *58*:723
combination therapy with cyclophosphamide and vincristine, *52*:593
combined with cyclophosphamide and/or vincristine in the treatment of various adenocarcinomas, *59*:425
combined with methotrexate and prednisolone in the treatment of hepatoma, *59*:1167
combined with hormones in the treatment of metastatic carcinoma of the female breast, *52*:743

comparative response of carcinoma of the rectum and of the colon to fluorinated pyrimidines, *53*:283
comparative studies of monthly courses versus weekly doses of, *53*:243
compared to adriamycin in the treatment of advanced colorectal cancer, *59*:405
compared with adriamycin in the treatment of advanced prostatic cancer, *59*:215
compared with cyclophosphamide in patients with advanced prostatic cancer, *59*:195
compared with cyclophosphamide in the treatment of bronchogenic cancer, *59*:1025
compared with mitomycin C using hepatic arterial infusion for liver metastases from colon cancer, *59*:401
comparison of, alone and in combination with mitomycin C, thioTEPA, and fluoxymesterone in patients with advanced cancer, *52*:597
comparison of oral and iv routes in the treatment of pancreatic cancer, *59*:1031
correlation of, distribution in rodents with toxicity and chemotherapy in man, *58*:777
5-day iv infusion after failure on weekly therapy in gastroenteric cancer, *59*:1177
determination of plasma levels in rats and man by isotope dilution-mass fragmentography, *59*:279
effect of concomitant drug treatment on toxic and therapeutic activity of, *56*:245
effect of, in 389 patients with cancer, Eastern Clinical Drug Evaluation Program, *52*:641
evaluation in the C1300 murine neuroblastoma model, *59*:975
for prostatic cancer in man, *59*:251
further clinical studies of, given by the multiple daily dose method in disseminated breast cancer, *57*:59
given by the multiple daily dose method in disseminated breast cancer, *51*:483
in glucose and saline: therapeutic effect and toxicity, *50*:683
intermittent intra-arterial infusion in outpatients, *50*:331
in the treatment of acute leukemia in children, *57*:335
in the treatment of colorectal carcinoma, *56*:563
in vitro screening of, *57*:463
lack of effect of warfarin alone or in combination with, on primary and metastatic L1210 leukemia and Adenocarcinoma 755, *55*:29
phase I study of azotomycin plus, in colon carcinomas, *54*:109
new model for studying the effects of, on the growth of the prostate gland in rats, *59*:185
phase I study, combined with adriamycin in the treatment of breast cancer and other solid tumors, *59*:1163
phosphoribosyl transferase in colon tumor and normal mucosa as an aid in adjuvant chemotherapy with, *58*:909
plus BCNU for disseminated gastrointestinal cancer, *56*:653
plus cyclophosphamide and vincristine: vincristine neuropathy, *58*:413
plus cyclophosphamide, compared with adriamycin in the treatment of advanced prostatic cancer, *59*:203
plus cytosine arabinoside in L1210 mouse leukemia, *51*:435
plus deuterium oxide in chemotherapy on transplantable mouse tumors, *50*:641
plus diethylstilbestrol versus diethylstilbestrol alone in the treatment of stage D prostatic adenocarcinoma, *59*:243
plus DTIC, vincristine, and BCNU given concomitantly in the treatment of solid tumors in man, *56*:107
plus methotrexate, adriamycin, and cyclophosphamide for adult solid tumors, *58*:943
plus methotrexate, vincristine, cyclophosphamide, and prednisone for disseminated adenocarcinoma, *56*:761
plus mitomycin C and cytosine arabinoside for advanced cancer in man, *56*:373
plus 100% oxygen inhalation for large bowel carcinoma, *58*:951
plus procarbazine in advanced carcinoma of the lung, *54*:369
plus radiation: an additive effect in bronchogenic carcinoma, *55*:253
treatment of MAC–13 and MAC–15, adenocarcinomas of the colon in mice, *59*:1083
used in potential test systems in animals to determine activity against prostatic cancer, *59*:175
versus CCNU in the treatment of stage D prostatic adenocarcinoma, *59*:243
Fluoxymesterone (NSC–12165)
combined with other agents in the treatment of patients with advanced cancer, *52*:597
compared with calusterone in advanced breast cancer, *58*:939
plus BCNU in the treatment of solid tumors, *57*:225
5-Formamido-1-β-D-ribofuranosylthioimidazole-4-carboxamide 2′,3′,5′–triformate, antitumor activity of, in a variety of animal tumors, *55*:229
Friend leukemia virus
effects of hydroxyurea and actinomycin D on several parameters of infection by, spleen focus-forming, *52*:557
in vivo antiviral properties of biologically active compounds, *50*:299

G

Gallium nitrate (NSC–15200), toxicity and antitumor activity in experimental rodent tumors, *59*:599
Gastrointestinal cancer *see* Carcinoma in man, gastrointestinal
Glial tumors *see* Carcinoma in man, brain
Glucose tolerance, patterns of iv, and insulin response in the treatment with streptozotocin in patients with cancer, *56*:61
β-Glucosidase (NSC–128056)
antitumor activity of amygdalin MF (laetrile) as a single agent and combined with, on a spectrum of transplantable rodent tumors, *59*:939
combined with amygdalin MF (laetrile), experimental studies of the antitumor activity of, *59*:951

β-Glucuronidase, urinary excretion of, after administration of streptozotocin to Fischer rats, *57*:235
Glutaminase-asparaginases, antineoplastic and toxic effects of *Acinetobacter* and *Pseudomonas*, *58*:829
Gompertz growth curve, estimation of tumor cell kill from, *59*:267
Griseofulvin (NSC–34533), inhibition of cilia regeneration and mitosis by, *56*:557
Guanazole (NSC–1895)
in the treatment of childhood leukemia, *58*:715
evaluation in the C1300 murine neuroblastoma model, *59*:975
phase I study of, in the treatment of various tumors, *59*:1117

H

Hadacidin (NSC–521778), clinical trial at the fractionated dose levels, *52*:425
Halopyrimidines, X-ray sensitization by (review), *58*:539
Head and neck carcinoma *see* Carcinoma in man, head and neck
Hearing function, effects of *cis*-dichlorodiammineplatinum(II) on, in man, *58*:871
HeLa cells
activity of some derivatives of daunorubicin in, *57*:269
biologic activity of some adriamycin derivatives, *58*:769
cytopathologic effects of mercenene on, *50*:655
effect of mannitol mustard on nuclear DNA content, *53*:115
molecular pharmacology of ricin and concanavalin A in, *58*:491
pharmacologic effects of 1,2:5,6–dianhydrogalactitol, *56*:593
Hematopoietic stem cells, altered sensitivity of, to 5-FU following endotoxin, cyclophosphamide, or irradiation, *58*:813
Hemolysis *see* Toxic reactions: animals
Heparin (NSC–145954), role of, in the treatment of carcinoma of the lung, *56*:783
Hepatic arterial infusion, for liver metastases from colon cancer: comparison of 5-FU and mitomycin C, *59*:401
Hepatocellular carcinoma *see* Carcinoma in man, liver
Herpes zoster, in acute leukemia after therapy with cytosine arabinoside, *53*:49
Hepatoma *see* Carcinoma in man, liver
Hexamethylmelamine (NSC–13875)
clinical evaluation of, *57*:51
effect of, on small cell carcinoma of the lung (phase II study), *58*:371
further experience with, in the treatment of carcinoma of the cervix, *57*:497
in the treatment of advanced cancer, *56*:505
plus methotrexate in the treatment of carcinoma of the lung, *55*:299
used in potential test systems in animals to determine activity against prostatic cancer, *59*:175
Hexestrol (NSC–9894), phase II clinical study of, *52*:751
L-*lyxo*-Hexopyranoside, 3-β-acetyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-10-methoxy-6,11-dioxo-1α-naphthacenyl-3-acetamido-2,3,6-trideoxy-, α-, compd. with isopropyl alcohol (1:1) (NSC–118714), toxicologic screening in rats, *59*:707
Histiocytosis X, childhood, response to procarbazine, *58*:719
Hodgkin's disease
advanced, treatment of, with vinblastine or procarbazine, *53*:39
antitumor activity of 1-methyl-1-nitrosourea in, *58*:135
BCNU in the treatment of advanced, *58*:383
cyclophosphamide therapy for children with, *51*:393
dibromodulcitol in the treatment of, *53*:377
effect of piposulfan on, *52*:433
effect of vincristine on, *52*:497
hexamethylmelamine in the treatment of, *56*:505
MOPP-resistant, bleomycin combined with CCNU in the treatment of, *59*:1147
possible radiation pericarditis in, *54*:199
response of fever of, to mechlorethamine, *53*:127
short-term sequential therapy with vinblastine and cyclophosphamide in, *55*:607
toxicity study of BCNU given orally, *58*:407
treatment of, with BCNU, *55*:599
Hydrazine sulfate (NSC–150114), in the treatment of various cancers, *59*:1151
Hydrocortisone (NSC–10483), development of immunity to L1210 leukemia in BDF_1 mice and effects of, *50*:55
6-Hydroxydopamine (NSC–233898), unorthodox therapy for murine neuroblastoma with, *59*:571
5-Hydroxypicolinaldehyde thiosemicarbazone (NSC–107392), clinical trials of, with special reference to its iron-chelating properties, *58*:207
Hydroxyprogesterone caproate (NSC–17592), effect of, on cancer of the prostate, *51*:41
Hydroxyprogesterone, effect of, on carcinoma of the prostate, *51*:41
Hydroxyurea (NSC–32065)
clinical and biochemical studies of high-dose intermittent therapy of solid tumors with, *54*:191
combined with vincristine in the treatment of metastatic renal cancer, *59*:1159
dose-schedule studies with, in malignant melanoma, *55*:277
effect of, on several parameters of infection by Friend spleen focus-forming virus, *52*:557
failure of, alone or plus prednisone in the treatment of acute myelocytic leukemia, *55*:199
intermittent therapy in malignant diseases, *53*:385
in therapy for nonresectable cancer of the lung, *52*:271
in the treatment of disseminated malignant melanoma, *56*:369
new model for studying the effects of, in the growth of the prostate gland in rats, *59*:185
phase II study of, in malignant melanoma, *51*:503
response in male and female mice with Taper liver tumor, *53*:325
single reversal trial of, in 91 patients with advanced cancer, *54*:53
studies on the absorption, distribution, and excretion of, in man, *55*:167
treatment in metastatic retinoblastoma, *52*:631

treatment of nonresectable cancer of the lung with, given intermittently, *55*:87
with irradiation for cervical carcinoma, *52*:601
N-Hydroxyurethan (NSC-83629), clinical studies of, *52*:635
Hyperalimentation, iv, chemotherapeutic response in patients given, *59*:437
Hypercalcemia, management of, complicating cancer, *55*:509
Hyperglycemia, due to prednisone or L-asparaginase plus prednisone, *56*:781
Hypernephroma, evaluation of 6-aminonicotinamide in the treatment of metastatic, *54*:175
Hyperthermia
and cancerous tissue water structure, *58*:296
as an adjuvant in the treatment of osteogenic sarcoma, *59*:257
effect of reserpine-induced, on lifespan in mouse L1210 leukemia, *58*:317
in the treatment of cancer, *58*:294
preliminary observations on temperature-enhanced drug uptake by leukemic leukocytes in vitro, *59*:985
Hypocholesteremic agents, effect of, on growth of transplantable animal tumors, *50*:25

I

ICRF–159 (NSC–129943)
blood clearance of, *55*:527
evaluation in the C1300 murine neuroblastoma model, *59*:975
phase I clinical trial of a single-dose and two weekly schedules of, *58*:393
phase I study of, in human solid tumors, *57*:185
phase II study of, in advanced colorectal cancer, *59*:761
used to enhance the effectiveness of daunorubicin or adriamycin against early mouse L1210 leukemia, *59*:689
Imidazole-4-carboxamide, aminothio, and derivatives, antitumor activity in a variety of animal tumors, *53*:165
Imidazole-4-carboxamide, 5-[3,3-bis(2-chloroethyl)-1-triazeno]- *see* BIC
Imidazole-4-carboxamide, 5-(3,3-dimethyl-1-triazeno)- *see* DTIC
Imidazole carboxamides, relationship of lipophilicity to activity against intracerebral murine Glioma 26, *59*:327
3,3′-Iminodi-1-propanol, dimethanesulfonate (ester), hydrochloride *see* Dimethanesulfonate
3,3′-Iminodi-1-propanol, dimethanesulfonate (ester), *p*-toluenesulfonate *see* 1-Propanol, 3,3′-iminodi-, dimethanesulfonate (ester), *p*-toluenesulfonate
Immune response
effect of 1,3,4-thiadiazole, 2,2′-(methylenediimino)bis- on tumor growth and, *58*:331
genetic alteration in tumor cells resulting in their escape from, *58*:431
Immunity, development of, to L1210 leukemia in BDF_1 mice and effects of therapy, *50*:55
Immunosuppression
activity of cycloleucine in mice, *56*:579
increased, of murine lymphatic tumors by 3(or 5)-aminopyrazole-4-carboxamide, *57*:3
mechanism of action of cancer chemotherapy drugs: an alternative hypothesis based on inhibition of immunologic function, *56*:559
prevention of cyclophosphamide, by BCG, *58*:931
Immunotherapy
current status of, *59*:901
inhibition of antilymphoma allograft response in normal and lethally irradiated mice by cyclophosphamide and isophosphamide, *59*:967
prostatic cancer treated with bacillus Calmette-Guerin, *59*:157
Indium nitrate, toxicity and antitumor activity in experimental rodent tumors, *59*:599
Infusion
continuous injection methods in biology, *51*:59
equipment and techniques for continuous, in humans and animals, *51*:49
Inosine dialdehyde (NSC–118994)
chemical assay to determine concentrations of, in biologic fluids, *59*:685
phase I study of, *59*:1007
used in potential test systems in animals to determine activity against prostatic cancer, *59*:175
Interferon, its inducers and some aspects of host resistance in malignancy, *58*:571
5-Iododeoxyuridine (NSC–39661)
bronchial artery infusion of, in bronchogenic carcinoma, *52*:263
intraventricular treatment in the treatment of progressive multifocal leukoencephalopathy, *57*:73
Insulin response, patterns of glucose tolerance and, in treatment with streptozotocin in patients with cancer, *56*:61
Isophosphamide (NSC–109724)
clinical trials of, results and side effects, *58*:889
evaluation in the C1300 murine neuroblastoma model, *59*:975
gas chromatographic method for the determination of plasma, *56*:721
human pharmacokinetic model for, *59*:877
inhibition of antilymphoma allograft response in normal and lethally irradiated mice by, *59*:967
in vitro activation of, by rat liver microsomes, *56*:663
phase I study of, *59*:751
phase II trial of, in patients with advanced breast cancer, *58*:861
renal dysfunction after treatment with isophosphamide, *58*:375
toxicity, protection with *N*-acetyl-L-cysteine against, and enhancement of therapeutic effect in early murine L1210 leukemia, *57*:299
used in potential test systems in animals to determine activity against prostatic cancer, *59*:175
Isopropylidene azastreptonigrin (NSC–62709)
comparative teratogenic effects of streptonigrin and, in the rat, *53*:23
comparison of biochemical effects of, with streptonigrin, *51*:19

K

Kaposi's sarcoma
actinomycin in the treatment of, *58*:49
effective treatment of, with DTIC, *57*:65
phase II clinical trials of BCNU and bleomycin in the treatment of, *57*:325
Kethoxal bis(thiosemicarbazone) *see* Butyraldehyde, 3-ethoxy-2-oxo-bis(thiosemicarbazone)
Krebiozin (NSC–8752), recurrent masses at sites of prior injections, *58*:249

L

L5178Y *see* Tumor systems in animals, leukemia, L5178Y
L cells *see* Cell lines
Lactate dehydrogenase
effect of 1,3-butanediol cyclic sulfite on, *50*:85
inhibition of, by sulfite-releasing compounds, especially 1,3-butanediol cyclic sulfite and α-anilino-α-toluene sulfonic acid sodium salt, *50*:89
Laetrile *see* Amygdalin MF
Laminar air flow rooms, use of, and microbial suppression to prevent infection in patients with cancer, *59*:1055
Lankacidin C (NSC–145118), antitumor and immunosuppressive activity against experimental tumors in mice, *59*:919
Lankacidin-group antibiotics, antitumor and immunosuppressive activities of, structure-activity relationships, *59*:919
Large bowel carcinoma *see* Carcinoma in man, colon
Last surviving cancer cell: the chances of killing it, *50*:541
Leucovorin *see* Citrovorum factor
Leukemia in man
adult
azotomycin: biologic fate in, *55*:47
chemotherapeutic evidence for viral agents in, and its chemotherapeutic consequences, *58*:595
acute
advanced, daunorubicin, vincristine, cytosine arabinoside, and prednisone combination therapy for, *59*:757
chemotherapy of (review), *55*:309
lymphocytic
5-azacytidine in the treatment of, *57*:319
clinical studies of 6-methylmercaptopurine riboside in, *51*:535
cyclophosphamide, vincristine, cytosine arabinoside, and prednisone combination chemotherapy for, *56*:543
cytosine arabinoside plus cyclophosphamide therapy for, *54*:255
intermittent therapy with 6-mercaptopurine and methotrexate given iv to patients with, *56*:535
phase I evaluation of cyclocytidine in the treatment of, *59*:389
prednisone therapy in, *58*:521
streptozotocin in the treatment of, *59*:443
treatment of, with L-asparaginase, *55*:269
myelocytic
absorption, distribution, and excretion of hydroxyurea in, *55*:167
adriamycin in the treatment of, *56*:237
5-azacytidine in the treatment of, *57*:319
clinical studies of 6-methylmercaptopurine riboside in, *51*:535
cyclophosphamide, vincristine, cytosine arabinoside, and prednisone combination chemotherapy for, *56*:543
cytosine arabinoside plus cyclophosphamide therapy for, *54*:255
cytosine arabinoside plus daunorubicin therapy in, *57*:485
cytosine arabinoside therapy in, *53*:59
development of herpes zoster in, after therapy with cytosine arabinoside, *53*:49
failure of hydroxyurea and prednisone in the treatment of, *55*:199
high-dose daunorubicin in the treatment of advanced, *56*:755
intermittent therapy with 6-mercaptopurine and methotrexate given iv to patients with, *56*:535
6-mercaptopurine and 6-methylmercaptopurine in patients with, *52*:315
phase I evaluation of cyclocytidine in the treatment of, *59*:389
plasma half-life of cytosine arabinoside in patients treated for, *55*:291
treatment of, with L-asparaginase, *55*:269
nonlymphocytic
5-azacytidine combined with methyl-GAG in the treatment of, *59*:1043
BCNU combined with cyclophosphamide in the remission maintenance of, *59*:537
daunorubicin combined with cytosine arabinoside, 6-thioguanine, prednisone, and vincristine in the treatment of, *59*:1131
prediction of the response of patients with, to cytosine arabinoside therapy, *56*:527
therapy for, with cytosine arabinoside, vincristine, and prednisone, *52*:305
chronic
granulocytic, treatment of, with piposulfan, *53*:121
lymphocytic
comparison of biochemical effects of isopropylidene azastreptonigrin with streptonigrin in leukocytes and erythrocytes of, *51*:19
phase I–II studies of mitoclomine in the treatment of, *59*:1173
myelocytic
chemotherapy for the terminal phase of, *58*:233
dibromodulcitol treatment in, *53*:379
dibromomannitol in previously treated patients with, and blastic transformation, *58*:223
dibromomannitol in the treatment of, *51*:9
effect of two new sulfonic acid esters of aminoglycols on chronic myelogenous leukemia, *56*:47
treatment of, with 3,3′-iminodi-1-propanol, dimethanesulfonate (ester), *p*-toluenesulfonate given orally, *56*:335

clinical trial of 5-hydroxypicolinaldehyde thiosemicarbazone, *58*:207
immunotherapy: quantitative aspects and adjuvant relationships to chemotherapy, *53*:3
childhood
acute
central nervous system, dibromodulcitol compared with cyclophosphamide as remission maintenance therapy in previously treated children with acute lymphocytic or acute undifferentiated leukemia: possible effectiveness in reducing the incidence of, *59*:989
chemotherapy of (review), *55*:309
chemotherapy with 6-azauridine, *53*:203
combination therapy with 6-mercaptopurine and allopurinol during induction and maintenance of remission of, *53*:53
comparison of cyclophosphamide and 6-mercaptopurine as therapy for, *51*:381
cyclophosphamide in the treatment of, *51*:389
cyclophosphamide plus cytosine arabinoside in the treatment of, *53*:299
cytosine arabinoside in the treatment of, *50*:287
evaluation of procarbazine in the treatment of, *57*:371
fluorometholone in the treatment of, *50*:339
5–FU and actinomycin D in the treatment of, *57*:355
lymphocytic
L-asparaginase plus azaserine in, *54*:47
BIC in the treatment of, *59*:371
comparison of cyclophosphamide and 6-mercaptopurine as therapy for, *51*:381
cytosine arabinoside plus L-asparaginase in the treatment of, *56*:363
daunorubicin versus daunorubicin plus prednisone versus daunorubicin plus vincristine plus prednisone in advanced, *56*:729
DTIC in the treatment of advanced, *56*:523
effectiveness of vincristine against refractory, *52*:473
efficacy and morbidity of daunorubicin plus vincristine and prednisone for remission induction of, *55*:79
guanazole in the treatment of, *58*:715
high-dose cyclophosphamide therapy in, *58*:417
methotrexate alone or combined with daunorubicin in the remission-maintenance treatment of, *59*:395
preliminary observations of VM–26 and VP–16–213 in, *59*:743
previously treated, dibromodulcitol compared with cyclophosphamide in the maintenance treatment of: possible effectiveness in reducing the incidence of central nervous system leukemia, *59*:989
response of, to repeated courses of vincristine, *51*:465
standard-dose cyclophosphamide vs high-dose cyclophosphamide vs cyclophosphamide combined with cytosine arabinoside in the maintenance treatment of, *59*:1097
7-substituted actinomycin D analogs tested against, *58*:35
tryptophan mustard in the treatment of, *52*:445
monocytic, vinblastine with or without prednisone in the treatment of, *59*:385
myelocytic
advanced daunorubicin in, *58*:661
effectiveness of vincristine against refractory, *52*:473
guanazole in the treatment of, *58*:715
tryptophan mustard in the treatment of, *52*:445
nonlymphocytic
preliminary observations of VM–26 and VP–16–213 in, *59*:743
undifferentiated, previously treated, dibromodulcitol compared with cyclophosphamide in the maintenance treatment of: possible effectiveness in reducing the incidence of central nervous system leukemia, *59*:989
remission induction in, with second course vincristine plus prednisone, *54*:113
response of, to repeated courses of vincristine, *51*:465
thiopurines in the treatment of, *52*:321
third and fourth remission induction with prednisone plus vincristine in, *54*:293
vincristine therapy for refractory, *52*:477
vincristine in the treatment of, *52*:469
chronic, chemotherapy with 6-azauridine, *53*:203
clinical trial of 5-hydroxypicolinaldehyde thiosemicarbazone, *58*:207
immunotherapy: quantitative aspects and adjuvant relationships to chemotherapy, *53*:3
Leukemia L5178Y *see* Tumor systems in animals, leukemia, L5178Y
Leukemia L1210 *see* Tumor systems in animals, leukemia, L1210
Leukocytes, cytogenic effects of 3-[bis(2-chloroethyl)amino]-4-methylbenzoic acid in human peripheral, *57*:29
Leukoencephalopathy, progressive multifocal, 5-iododeoxyuridine in the treatment of, *57*:73
Levamisole (NSC–177023)
effect of, on in vitro human lymphocyte transformation, *58*:167
effects of, alone or combined with BCNU, on DNA synthesis by lymphocytes from immunosuppressed C57BL mice, *59*:531
effects of, in experimental tumor systems, *59*:697
Lewis lung carcinoma *see* Tumor systems in animals, carcinoma, Lewis lung
Linear array
management of the National Cancer Institute's drug research program through application of, *54*:303
proposal for the National Cancer Institute cancer chemotherapy program, *50*:461
Liver carcinoma *see* Carcinoma in man, liver
Liver metastasis, from colon cancer, comparison of mitomycin C and 5–FU using hepatic arterial infusion, *59*:401
Lung
hazards of lymphography, *52*:107

lymphography of, *52*:99
toxicity induced by treatment with bleomycin, *56*:343
Lung cancer *see* Carcinoma in man, lung
Lymphangiography *see* Lymphography
Lymphatic system
dynamics of normal and abnormal, as studied with contrast media, *52*:31
gross and microscopic anatomy vessels and lymphaticovenous communications, *52*:1
physiologic function of, *52*:25
structure of, *52*:21
Lymphoblastic leukemia *see* Leukemia in man, lymphocytic
Lymphocyte transformation, effect of levamisole on, in man, *58*:167
Lymphocytic leukemia *see* Leukemia in man, acute, lymphocytic
Lymphography
clinical experiences with, *52*:189
contribution of, to our understanding of lymphoma, *52*:213
correlation between lymphangiography and clinical status of patients with, *52*:205
correlation with clinical status of patients with lymphoma, *52*:205
diagnostic criteria for interpretation of malignant neoplasia, *52*:125
gross and microscopic anatomy of lymphatic vessels and lymphaticovenous communications, *52*:1
hazards of, *52*:77
interpretation of, *52*:147
interpretation of (discussion), *52*:201
interpretation of normal and abnormal, *52*:119
of normal and abnormal lymphatic systems, *52*:31
pulmonary function studies, *52*:99
pulmonary hazards of, *52*:107
pulmonary oil embolism as a hazard of, *52*:81
roentgenologic aspects of lymphoma as seen in, *52*:171
technical aspects of, *52*:59
technique of, *52*:65
technique of (discussion), *52*:73
typical fatal reactions after, *52*:113
usefulness and accuracy of, in lymphoma, *52*:157
Lymphoma
actinomycin D in the treatment of, *58*:49
AK, model, *57*:1
Burkitt's *see* Burkitt's lymphoma
chlorambucil treatment in patients with advanced, *52*:661
contribution of lymphangiography to understanding of, *52*:213
cis-dichlorodiammineplatinum(II) in the treatment of, *59*:621
DTIC in the treatment of, *56*:667
effect of piposulfan on malignant, *52*:433
generalized cyclophosphamide therapy for children with, *51*:393
histiocytic and poorly differentiated, streptozotocin in the treatment of, *59*:443
lymphographic aspects of, *52*:171
malignant, effect of cyclophosphamide on 127 patients with, *50*:265
malignant, treated with two new methanesulfonic acid esters of aminoglycols, *57*:159
6-mercaptopurine treatment in patients with advanced, *52*:655
prednisone therapy in, *58*:521
private practice of medical oncology in, *58*:759
prognosis of diffuse non-Hodgkin's, treated with COP or cyclophosphamide alone, *59*:421
usefulness and accuracy of lymphangiography in, *52*:157
vinblastine plus vincristine given in intensive 3-day courses for, *57*:481
VM-26 in the treatment of patients with, *56*:71
weekly doses of vinblastine plus vincristine in malignant, *57*:477
Lymphosarcoma
BCNU in the treatment of advanced, *58*:383
total-body radiation therapy for disseminated (pilot study), *58*:401

M

Macromycin (NSC–170105)
in vitro studies on: effects on cultured TA3Ha and L1210 cells, *58*:181
modification of transplantability and tumor growth following treatment of L1210 leukemia and TA3Ha cells with, *57*:501
Malignant melanoma *see* Melanoma
Mannitol mustard (NSC–9698), effect on nuclear DNA content and birefringence of HeLa and Chinese hamster cells, *53*:115
Mass fragmentography, isotope dilution, determination of 5–FU plasma levels in rats and man by, *59*:279
Mechlorethamine (NSC–762)
alone or with demecolcine in pretreatment of V × 2 carcinoma undergoing isolation perfusion, *56*:175
effect of hyperbaric oxygen and, on Ehrlich ascites tumor cells, *52*:405
effect of, on kinetic behavior of cultured L1210 leukemic cells, *51*:7
in vitro screening of, *52*:463
response of fever of Hodgkin's disease, *53*:127
Melanoma
BIC in the treatment of metastatic malignant, *56*:671
clinical trials with DTIC in malignant, *54*:119
cytologic studies on human cells in tissue culture after exposure to five chemotherapeutic agents, *52*:543
disseminated malignant, comparative study of methyl-CCNU with cyclophosphamide and DTIC with vincristine in patients with, *59*:451
dose-schedule studies with hydroxyurea in, *55*:277
DTIC given iv in the treatment of malignant, in Uganda, *55*:143
DTIC treatment in patients with disseminated, *57*:83
evaluation of DTIC, melphalan, and hydroxyurea in the treatment of disseminated malignant, *56*:369
further study of trimethylcolchicinic acid, methyl ether, *d*-tartrate in patients with malignant, *56*:263
intermittent treatment of, with high-dose DTIC, *55*:175

large intermittent iv doses of cyclophosphamide in the treatment of metastatic malignant, *54*:365
malignant, nordihydroguaiaretic acid in the treatment of, *53*:147
malignant, treatment of, with vinblastine, procarbazine, and actinomycin D, *59*:767
metabolism of DTIC in, *56*:465
metastatic, adriamycin in the treatment of, *59*:1181
metastatic malignant, treatment of, with DTIC plus cyclophosphamide plus vincristine, *56*:357
6α-methylpregn-4-ene-3,11,20-trione, phase I clinical study of, *50*:671
phase I study of guanazole in, *59*:1117
regression of intradermal malignant, after intralesional injection of *Mycobacterium bovis* strain BCG, *56*:659
treatment of malignant, with camptothecin, *56*:103
phase II study of hydroxyurea in malignant, *51*:503
Melphalan (NSC–8806)
administration in osteogenic sarcoma: an evaluation of dosage schedules, *55*:151
alone or with demecolcine or vinblastine, in pretreatment of V × 2 carcinoma undergoing isolation perfusion, *56*:175
cytologic studies on human melanoma cells in tissue culture, *52*:543
in the treatment of advanced breast cancer, *50*:271
in the treatment of disseminated malignant melanoma, *56*:369
in the treatment of multiple myeloma, *56*:563
multiple myeloma resistant to, treated with cyclophosphamide and prednisone, with or without chloroquine, *59*:557
plus mitomycin C and vincristine in the treatment of osteogenic sarcoma, *55*:189
therapy for children with metastatic neuroblastoma, *52*:293
treatment of MAC–13 and MAC–15, adenocarcinomas of the colon in mice, *59*:1083
treatment in metastatic retinoblastoma, *52*:631
2-Mercapto-3-hydroxypropranolol, inhibitory effect of, on growth of transplantable cancers in mice, *53*:195
6-Mercaptopurine (NSC–755; 6-MP)
compared with cyclophosphamide as therapy for acute leukemia in children, *51*:381
development of a microbiologic assay capable of detecting cytosine arabinoside in body fluids in the presence of, *59*:515
differential sensitivities of normal hematopoietic and resistant L1210 leukemia colony-forming cells to, *52*:251
effect of, in 290 patients with advanced cancer: Eastern Clinical Drug Evaluation Program, *52*:655
given intermittently in high doses, phase II study, *54*:31
given iv at weekly intervals to patients with advanced cancer, *51*:277
in the treatment of acute childhood leukemia, *52*:321
in the treatment of terminal chronic myelocytic leukemia, *58*:233
kinetic parameters and cell cure in Carcinoma 755, *53*:169
plus allopurinol during remission of acute leukemia in children, *53*:53
plus cytosine arabinoside in L1210 mouse leukemia, *51*:435
plus deuterium oxide in chemotherapy of transplantable mouse tumors, *50*:641
plus methotrexate intermittent therapy given iv to adults with acute leukemia, *56*:535
plus 6-methylmercaptopurine riboside in neuroblastoma, *58*:683
plus 6-methylmercaptopurine riboside in patients with acute leukemia and metastatic cancer, *52*:315
plus 6-methylmercaptopurine riboside in therapy of Ehrlich ascites carcinoma, *51*:101
plus 6-methylthiomercaptopurine ribonucleoside in chemotherapy of L1210 leukemia, *51*:111
spleen colony studies of L1210 leukemia: sensitivity of L1210 and L1210/6–MP to triazenoimidazolecarboxamides, *52*:393
6-Mercaptopurine riboside (NSC–4911), acute leukemia in children, after remission on prednisone, *52*:321
Mercenene, cytopathologic effects on Krebs 2 carcinoma in CF_1 mice and HeLa and human amnion cell lines, *50*:655
Metabolic conditioning and actuation: experimental approaches to cancer chemotherapy involving combinations of metabolites and antimetabolites, *58*:471
DL-Metasarcolysin (NSC–27381), preliminary clinical trial of, for advanced carcinoma of the breast, *52*:413
Metastases
cancer chemotherapy screening with experimental tumors which metastasize to lymph nodes, *54*:311
effect of some drugs on tumor dissemination and, *54*:79
Methasquin (NSC–122870)
dosage schedules in L1210 leukemia and toxicity, *55*:123
toxicologic studies of the antifolate, in experimental animals, *55*:35
Methotrexate (NSC–740)
activity against human tumor xenografts in immune-deprived mice, *58*:645
alone and in combination with daunorubicin in the remission-maintenance treatment of acute lymphocytic leukemia, *59*:395
analysis of the effects of, on cell cycle kinetics, *59*:847
assay for citrovorum factor in the presence of, *59*:935
combined with bleomycin and vincristine plus radiation therapy in the treatment of non-oat cell bronchogenic cancer, *59*:377
combined with cytosine arabinoside and cyclophosphamide in the treatment of advanced breast and lung cancer, *59*:1091
combined with 5–FU and prednisolone in the treatment of hepatoma, *59*:1167
cytologic studies on human melanoma cells in tissue culture, *52*:543
development of a microbiologic assay capable of detecting cytosine arabinoside in body fluids in the presence of, *59*:515
dosage schedules in L1210 leukemia and toxicity, *55*:123
effect of day of dosage omission on survival time in the regularly scheduled treatment of L1210 leukemia, *56*:25
effect of different doses of, on drug resistance in mice with L1210 leukemia, *56*:473

equipment and techniques of continuous infusion of, in humans and animals, *51*:49
high-dose, with citrovorum factor rescue in the treatment of metastatic bone tumors, *58*:275
in squamous cell carcinoma of the head and neck, intermittent iv therapy, *51*:69
intermittent parenteral, therapy for carcinoma of the lung, *51*:475
interspecies correlation of plasma concentration history of, *54*:95
in the treatment of advanced epidermoid carcinoma of the uterine cervix, *57*:429
in the treatment of head and neck cancer, toxicity of 24-hour infusion of, and protection by citrovorum factor in patients with epidermoid carcinomas, *51*:305
intrathecal injection of, in transplanted brain tumors, *51*:1
intrathecal, therapy for brain tumors in children, *52*:257
kinetic model for the disposition and metabolism of moderate and high-dose, in man, *59*:811
L1210 leukemia death in vivo after administration of, *53*:273
low dosage, and cyclophosphamide for solid tumors, *54*:41
malignant carcinoid: effect of parenteral therapy alone and combined with cyclophosphamide orally, *51*:239
phase II study of, in solid tumors, *51*:471
plus adriamycin, cyclophosphamide, and 5-FU for advanced solid tumors, *58*:943
plus BCNU in the treatment of advanced solid tumors, *56*:751
plus cyclophosphamide in the treatment of cervical carcinoma, *53*:255
plus cytosine arabinoside, DTIC, and BCNU in advanced L1210 leukemia, *57*:291
plus cytosine arabinoside in L1210 mouse leukemia, *51*:435
plus 5-FU, vincristine, cyclophosphamide, and prednisone for disseminated adenocarcinoma, *56*:761
plus hexamethylmelamine in the treatment of carcinoma of the lung, *55*:299
plus 6-mercaptopurine intermittent therapy given iv to adults with acute leukemia, *56*:535
plus radiotherapy in the treatment of advanced carcinoma of the head and neck, *56*:745
treatment of MAC-13 and MAC-15, adenocarcinomas of the colon in mice, *59*:1083

Methyl-CCNU (NSC–95441)
alone or combined with cyclophosphamide in the treatment of advanced gastrointestinal cancer, *59*:1161
combined with cyclophosphamide and vincristine in the treatment of small cell carcinoma of the lung in a 3-week schedule, *59*:1127
combined with cyclophosphamide in a comparative study with DTIC plus vincristine in patients with disseminated malignant melanoma, *59*:451
compared to BCNU and CCNU with regard to sensitivity of colony-forming cells of hemopoietic tissue, Lewis lung carcinoma, and B16 melanoma, *59*:929
compared with CCNU in advanced bronchogenic carcinoma, *58*:913
cure of metastatic Lewis lung carcinoma with, and surgery-chemotherapy, *56*:183
in the treatment of lung cancer, *57*:419
phase II study, in the treatment of various carcinomas, sarcomas, and lymphomas, *59*:1021
treatment of MAC-13 and MAC-15, adenocarcinomas of the colon in mice, *59*:1083

Methylcholanthrene (NSC–21970), neoplastic effect of, on human prostate in organ culture, *59*:67

2,2′-(Methylenediimino)bis-1,3,4-thiadiazole *see* 1,3,4-Thiadiazole, 2,2′-(methylenediimino)bis-

Methyl-GAG (NSC–32946)
combined with 5-azacytidine in previously treated adults with acute nonlymphocytic leukemia, *59*:1043
effectiveness of, administered im, *58*:689
in the treatment of esophageal cancer, *55*:209

3′3′-(Methylimino)di-1-propanol, dimethanesulfonate, hydrochloride (NSC–84641), effect of, on chronic myelogenous leukemia, *56*:47

6-Methylmercaptopurine riboside (NSC–40774)
clinical studies of, in acute leukemia, *51*:535
plus 6-mercaptopurine in chemotherapy of L1210 leukemia, *51*:111
plus 6-mercaptopurine in neuroblastoma, *58*:683
plus 6-mercaptopurine in patients with acute leukemia and metastatic cancer, *52*:315
plus 6-mercaptopurine in therapy of Ehrlich ascites carcinoma, *51*:101

Methyl methanesulfonate (NSC–50256), phase I clinical study, *50*:675

1-Methyl-1-nitrosourea (NSC–23909)
a discussion of the apprehensions concerning experimental and clinical use of, *59*:888
experimental and clinical studies of the antitumor activity of, *58*:135
potential hazards associated with the use of, *58*:617

7α-Methyl-19-nortestosterone (NSC–69948), preliminary dose-response studies of, in patients, *50*:335

6α-Methylpregn-4-ene-3,11,20-trione (NSC–17256)
phase I clinical study of, *50*:671
phase II study of, *55*:265

6-Methylthiopurine ribonucleoside *see* 6-Methylmercaptopurine ribonucleoside

Methyltrienolone (NSC–92858), antitumor efficacy and toxicity in advanced breast cancer, *54*:453

Meturedepa (NSC–51325), effect of, in 233 patients with advanced cancer: Eastern Clinical Drug Evaluation Program, *52*:667

Microbiologic assays
activity of adriamycin in, *55*:221
(α*S*,5*S*)-α-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid, reversal studies, *57*:141
BCNU, and assays, *51*:213
for cytosine arabinoside, *54*:393
for cytosine arabinoside in biologic materials containing other antitumor or antibacterial drugs, *55*:557
inhibition of cilia regeneration by antineoplastic agents, *55*:531
of mithramycin in mice, *58*:311
metabolism of azotomycin, *55*:47

radiosensitization of bacteria by cytosine arabinoside, *51*:229
sensitivity of resting and dividing cells, *54*:137
Microculture of human brain tumors, *54*:9
Microsomes, in vitro activation of isophosphamide by rat liver, *56*:663
Mimosine (NSC–69188), effect of tumor type and route of administration on the antitumor activity of, *57*:41
Mithramycin (NSC–24559)
chemotherapeutic response of human glial tumor cells cultured in cerebrospinal fluid, *51*:201
microbiologic assay and tissue distribution of, in mice, *58*:311
Mitoclomine (NSC–114575), phase I–II trials in chronic lymphocytic leukemia, *59*:1173
Mitogillin (NSC–69529), evaluation of, in the treatment of naturally occurring canine neoplasms, *55*:101
Mitomalcin (NSC–113233), toxicology studies with, in dogs, *54*:217
Mitomycin C (NSC–26980)
clinical experience with, *54*:195
clinical studies in colorectal cancer, *53*:287
combined with other agents in the treatment of patients with advanced cancer, *52*:597
compared to 5-FU using hepatic arterial infusion for liver metastases from colon cancer, *59*:401
effect of pyridoxal phosphate on toxicity and antitumor activity of, in rats, *50*:313
effects of, in 346 patients with advanced cancer: Eastern Clinical Drug Evaluation Program, *52*:675
evaluation of dosage schedule of, in children, *55*:285
intermittent dose schedule of, in solid tumors, *56*:151
in the treatment of metastatic osteogenic sarcoma, *53*:297
oral activity of, on Walker 256 (intramuscular) tumor, *52*:389
plus 5-FU and cytosine arabinoside for advanced cancer in man, *56*:373
plus phenylalanine mustard and vincristine in the treatment of osteogenic sarcoma, *55*:189
treatment of MAC-13 and MAC-15, adenocarcinomas of the colon in mice, *59*:1083
Mitosis
inhibition of cilia regeneration by antineoplastic agents: delay of band migration by vinblastine, griseofulvin, and β-peltatin, *56*:557
use of inhibitors of, in pretreatment of V × 2 carcinoma undergoing isolation perfusion with alkylating agents, *56*:175
Mouse sarcoma viruses, chemotherapeutic response of epithelial tumors produced by implantation of a nonproducer line of virus-transformed BALB-3T3 cells, *57*:149
6–MP *see* 6-Mercaptopurine
Multiple myeloma *see* Myeloma, multiple
Mutation, in tumor cells resulting in their escape from the immune response, *58*:431
Mycophenolic acid (NSC–129185)
clinical trial with, *56*:221
metabolic studies in man with, *56*:229
preliminary clinical trials, *56*:83
Myeloblastic leukemia *see* Leukemia in man, acute, myelocytic
Myeloblastic transformation, in refractory chronic myelocytic leukemia, *58*:223
Myelocytic leukemia *see* Leukemia in man, acute, myelocytic
Myelogenous leukemia *see* Leukemia in man, acute, myelocytic
Myeloma, multiple
alkylator-resistant, adriamycin in the treatment of, *59*:345
combination therapy with 6-thioguanine and azaserine for, *51*:234
intermittent high-dose prednisone therapy for, *51*:171
procarbazine in the treatment of, *54*:245
resistant to melphalan, treated with cyclophosphamide and prednisone with or without chloroquine, *59*:557
DL-*ortho*-sarcolysin in the treatment of multiple myeloma, *51*:517
treated with cyclophosphamide or melphalan, *56*:563

N

NADase, effect of BCNU and cyclophosphamide in normal and leukemic mouse tissues, *52*:569
NAD glycohydrolase *see* NADase
Nandrolone phenylpropionate (NSC–23162E), effect of, on the bone marrow suppression caused by cyclophosphamide: a clinical trial, *58*:867
National Cancer Institute, management of drug research program through application of the linear array concept, *54*:303
NDGA *see* Nordihydroguaiaretic acid
Neocarzinostatin (NSC–69856), an antitumor antibiotic effective against ascitic L1210 leukemia in mice, *50*:79
Nephroblastoma *see* Wilms' tumor
Neuroblastoma
combination intermittent chemotherapy for patients with disseminated, *56*:499
combination therapy including vincristine for, *52*:489
cyclophosphamide therapy for children with, *51*:399
daunorubicin in the treatment of metastatic, *54*:283
effect of vincristine on, *52*:497
in children, advanced stage IV, adriamycin combined with DTIC in the treatment of, *59*:1015
in children, BIC in the treatment of, *59*:371
in children, DTIC in the treatment of, *59*:351
response and survival of patients with metastatic, after combination chemotherapy with adriamycin, cyclophosphamide, and vincristine, *58*:365
L-sarcolysin therapy for children with metastatic neuroblastoma, *52*:293
treatment of, in children by a cyclic program of vincristine and cyclophosphamide, *51*:411
trials with cyclophosphamide alone, vincristine plus cyclophosphamide, 6-mercaptopurine plus 6-methylmercaptopurine riboside, and cytosine arabinoside alone, *58*:683
uracil mustard therapy for children with metastatic, *52*:287
Nitrogen mustard *see* Mechlorethamine

Nitroheterocyclic drugs, as selective radiosensitizers of hypoxic mammalian cells, *58*:559
Nitromin (NSC–10107), after surgery in the treatment of stomach and bronchial carcinoma, *56*:35
Nitrosourea compounds
effectiveness of, as a function of their lipid solubility in the chemotherapy of experimental rat brain tumors, *58*:787
quantitative structure-activity relationships of, in the treatment of L1210 leukemia, *56*:443
Nordihydroguaiaretic acid (NSC–4291), in the treatment of malignant melanoma, *53*:147
NSC–739 *see* Aminopterin
NSC–740 *see* Methotrexate
NSC–742 *see* Azaserine
NSC–749 *see* 8-Azaguanine
NSC–750 *see* Busulfan
NSC–752 *see* 6-Thioguanine
NSC–755 *see* 6-Mercaptopurine
NSC–757 *see* Colchicine
NSC–762 *see* Mechlorethamine
NSC–1026 *see* Cycloleucine
NSC–1390 *see* Allopurinol
NSC–1402 *see* 3(or 5)-Aminopyrazole-4-carboxamide
NSC–1759 *see* Testosterone enanthate
NSC–1895 *see* Guanazole
NSC–3053 *see* Actinomycin D
NSC–3063 *see* 4-Deoxypyridoxine hydrochloride
NSC–3070 *see* Diethylstilbestrol
NSC–3083 *see* Chlorambucil
NSC–3096 *see* Demecolcine
NSC–3590 *see* Citrovorum factor
NSC–4291 *see* Nordihydroguaiaretic acid
NSC–4911 *see* 6-Mercaptopurine riboside
NSC–6396 *see* ThioTEPA
NSC–7365 *see* DON
NSC–8415 *see* Butyric acid
NSC–8752 *see* Krebiozin
NSC–8806 *see* Melphalan
NSC–9698 *see* Mannitol mustard
NSC–9700 *see* Testosterone
NSC–9706 *see* Triethylene melamine
NSC–9717 *see* Tris(2,2-dimethyl-1-aziridinyl)phosphine
NSC–9894 *see* Hexestrol
NSC–9895 *see* Estradiol
NSC–9900 *see* Prednisolone
NSC–9902 *see* Ricin
NSC–10023 *see* Prednisone
NSC–10107 *see* Nitromin
NSC–10483 *see* Hydrocortisone
NSC–12165 *see* Fluoxymesterone
NSC–12198 *see* Dromostanolone propionate
NSC–13875 *see* Hexamethylmelamine
NSC–14210 *see* Phenylalanine mustard
NSC–14575 *see* 9-Ethyl-6-mercaptopurine
NSC–15197 *see* Thallium chloride
NSC–15200 *see* Gallium nitrate
NSC–15780 *see* Amygdalin MF
NSC–164011 *see* Rubidazone
NSC–170898 *see* VC-51
NSC–17256 *see* 6α-Methylpregn-4-ene-3,11,20-trione
NSC–17592 *see* Hydroxyprogesterone caproate
NSC–17663 *see* Alanine mustard
NSC–19893 *see* 5-Fluorouracil
NSC–19962 *see* Carbestrol
NSC–21206 *see* 6-Aminonicotinamide
NSC–21970 *see* 3-Methylcholanthrene
NSC–23162E *see* Nandrolone phenylpropionate
NSC–23759 *see* Δ^1-Testololactone
NSC–23909 *see* 1-Methyl-1-nitrosourea
NSC–24559 *see* Mithramycin
NSC–24818 *see* Podophyllotoxin
NSC–24819 *see* β-Peltatin
NSC–25485 *see* Strophanthin G
NSC–26271 *see* Cyclophosphamide
NSC–26980 *see* Mitomycin C
NSC–27381 *see* DL-Metasarcolysin
NSC–27640 *see* 5-Fluorodeoxyuridine
NSC–29630 *see* Dichloromethotrexate
NSC–32065 *see* Hydroxyurea
NSC–32074 *see* 6-Azauridine
NSC–32946 *see* Methyl-GAG
NSC–33001 *see* Fluorometholone
NSC–33669 *see* Emetine
NSC–34462 *see* Uracil mustard
NSC–34533 *see* Griseofulvin
NSC–35443 *see* Papaverine
NSC–36354 *see* Trimethylcolchicinic acid methyl ether
NSC–38270 *see* A-649
NSC–39069 *see* Dihydroxybusulfan
NSC–39661 *see* 5-Iododeoxyuridine
NSC–40774 *see* 6-Methylmercaptopurine riboside
NSC–42076 *see* SPG-827
NSC–45383 *see* Streptonigrin
NSC–45384 *see* Streptonigrin methyl ester
NSC–45388 *see* DTIC
NSC–45624 *see* Sodium thiosulfate
NSC–47774 *see* Piposulfan
NSC–49842 *see* Vinblastine
NSC–50256 *see* Methyl methanesulfonate
NSC–51095 *see* Ammonium, trimethylpurin-6-yl chloride
NSC–51325 *see* Meturedepa
NSC–51954 *see* A-6413
NSC–52947 *see* Pactamycin
NSC–56054 *see* Pseudourea
NSC–56410 *see* Porfiromycin
NSC–56654 *see* Azotomycin
NSC–57199 *see* DL-*ortho*-Sarcolysin
NSC–58404 *see* *N*-diazoacetylglycine hydrazide
NSC–58514 *see* Chromomycin A_3
NSC–59272 *see* Reserpine
NSC–59729 *see* Sparsomycin
NSC–59813 *see* Warfarin
NSC–60195 *see* 1,3-Butanediol cyclic sulfite
NSC–62164 *see* Bretylium tosylate
NSC–62403 *see* Tryptophan mustard
NSC–62512 *see* 2-(Dimethylamino)-3′4′-dihydroxyacetophenone hydrochloride
NSC–62709 *see* Isopropylidine azastreptonigrin
NSC–63701 *see* Toyocamycin
NSC–63878 *see* Cytosine arabinoside
NSC–65346 *see* Sangivamycin

NSC–66761 *see* Terephthalanilide, 2-amino-4′,4″-bis(5-methyl-2-imidazolin-2-yl)-
NSC–67574 *see* Vincristine
NSC–67934 *see* 2,3-Dihydroxypropanal
NSC–68075 *see* Thalicarpine
NSC–68626 *see* 1-Acetyl-2-picolinoylhydrazine
NSC–69188 *see* Mimosine
NSC–69529 *see* Mitogillin
NSC–69856 *see* Neocarzinostatin
NSC–69945 *see* Phosphorodiamidic acid, *N,N*-bis(2-chloroethyl)-cyclohexylamine salt
NSC–69948 *see* 7α-Methyl-19-nortestosterone
NSC–71795 *see* Ellipticine
NSC–71964 *see* [*p*-[Bis(2-chloroethyl)amino]phenyl]acetic acid
NSC–72274 *see* SPI-77
NSC–75520 *see* 2′-Deoxy-5-(trifluoromethyl)uridine
NSC–77213 *see* Procarbazine
NSC–77622 *see* Deluteval 2x
NSC–79019 *see* 2-Oxopropanal
NSC–79037 *see* CCNU
NSC–81430 *see* Cyproterone acetate
NSC–82116 *see* Butyraldehyde, 3-ethoxy-2-oxo-bis(thiosemicarbazone)
NSC–82151 *see* Daunorubicin
NSC–82196 *see* BIC
NSC–82260 *see* Tenuazonic acid, *N,N′*-dibenzylethylene diamine
NSC–82388 *see* Pyridoxal phosphate
NSC–83629 *see* *N*-hydroxyurethan
NSC–84641 *see* 3,3′-(Methylimino)di-1-propanol dimethylsulfonate, hydrochloride
NSC–85998 *see* Streptozotocin
NSC–87419 *see* Cyclohexylisocyanate
NSC–88536 *see* Calusterone
NSC–89199 *see* Estramustine phosphate
NSC–89681 *see* Endotoxin
NSC–90255 *see* Triton WR-1339
NSC–90636 *see* Vinleurosine sulfate
NSC–92338 *see* Chlormadinone acetate
NSC–92858 *see* Methyltrienolone
NSC–93415 *see* Diphenamid
NSC–94100 *see* Dibromomannitol
NSC–95441 *see* Methyl-CCNU
NSC–100880 *see* Camptothecin
NSC–101088 *see* Withaferin A
NSC–102063 *see* Tetramisole
NSC–102498 *see* 5-Carbamyl-L-cysteine
NSC–102627 *see* Dimethanesulfonate
NSC–102816 *see* 5-Azacytidine
NSC–104469 *see* Phenesterin
NSC–104800 *see* Dibromodulcitol
NSC–104801 *see* Cytembena
NSC–107392 *see* 5-Hydroxypicolinaldehyde thiosemicarbazone
NSC–107455 *see* Poricin
NSC–109229 *see* L-Asparaginase
NSC–109724 *see* Isophosphamide
NSC–111180 *see* *N*-Acetyl-L-cysteine
NSC–112259 *see* Estradiol mustard
NSC–112682 *see* 1,1-Diphenyl-2-propynyl cyclohexanecarbamate
NSC–112846 *see* Quinaspar
NSC–112907 *see* Tetrahydrouridine
NSC–113233 *see* Mitomalcin
NSC–114575 *see* Mitoclomine
NSC–116785 *see* Phenester
NSC–118436 *see* Phosphine oxide, tris(2,2-dimethyl-1-aziridinyl)
NSC–118714 *see* L-*lyxo*-Hexopyranoside, 3-β-acetyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-10-methoxy-6,11-dioxo-1α-naphthacenyl-3-acetamido-2,3,6-trideoxy-, α-, compd. with isopropyl alcohol (1:1)
NSC–118994 *see* Inosine dialdehyde
NSC–119875 *see* *cis*-Dichlorodiammineplatinum(II)
NSC–120949 *see* Poly IC
NSC–122402 *see* Dimethanesulfonate sugar derivative
NSC–122758 *see* Vitamin A acid
NSC–122819 *see* VM-26
NSC–122870 *see* Methasquin
NSC–123018 *see* 6-Dehydro-6,17-α-dimethylprogesterone
NSC–123127 *see* Adriamycin
NSC–125066 *see* Bleomycin
NSC–128056 *see* β-Glucosidase
NSC–129185 *see* Mycophenolic acid
NSC–129220 *see* Anhydro-ara-C
NSC–129943 *see* ICRF-159
NSC–130998 *see* *p*-Carboxycarbanilic acid, *N*-[*p*-[bis(2-chloroethyl)amino]phenyl] ester
NSC–132313 *see* 1,2:5,6-Dianhydrogalactitol
NSC–134679 *see* Carbazilquinone
NSC–135758 *see* Compound 593A
NSC–139105 *see* Triazinate
NSC–140115 *see* 4,4′-Biphenyldisulfonic acid compd. with 3,3′-(methylamino)di-1-propanol, dimethanesulfonate (ester)
NSC–140117 *see* 1-Propanol, 3,3′-iminodi-, dimethanesulfonate (ester), *p*-toluenesulfonate
NSC–141540 *see* VP-16-213
NSC–143017 *see* Aluminum nitrate
NSC–143019 *see* 1,3,4-Thiadiazole, 2,2′-(methylenediimino)bis-
NSC–143114 *see* Daunomycin-semicarbazone
NSC–143496 *see* Daunomycin, *N*-(butylcarbamoyl)-
NSC–143504 *see* Concanavalin A
NSC–143969 *see* Tilorone
NSC–145118 *see* Lankacidin C
NSC–145668 *see* Cyclocytidine
NSC–145669 *see* 2,3-Dihydro-2-(1-naphthyl)-4(1*H*)-quinazolinone
NSC–145954 *see* Heparin
NSC–146171 *see* 3-*N,N*-bis(2-chloroethylamino)-*p*-toluic acid
NSC–146268 *see* 2-Thio-6-azauridine
NSC–149584 *see* Adriamycin, 14-octanoate, hydrochloride
NSC–150014 *see* Hydrazine sulfate
NSC–163501 *see* L-[α*S*,5*S*]-α-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid
NSC–166641 *see* Anhydro-ara-5-fluorocytidine
NSC–166721 *see* 4-Carbethoxy-5-(3,3-dimethyl-1-triazeno)-2-phenylimidazole
NSC–166722 *see* 4-Carbethoxy-5-(3,3-dimethyl-1-triazeno)-2-methylimidazole
NSC–169533 *see* Daunorubicin-DNA

NSC–169534 *see* Adriamycin-DNA
NSC–169774 *see* 2-Bromo-α-ergocryptine
NSC–170105 *see* Macromycin
NSC–170898 *see* VC-51
NSC–172755 *see* Butocin
NSC–176324 *see* (α5,4*S*,5*R*)-α-Amino-3-chloro-4-hydroxy-4,5-dihydro-5-isoxazoleacetic acid
NSC–177023 *see* Levamisole
NSC–180024 *see* Carminomycin
NSC–187208 *see* Chloroquine
NSC–233898 *see* 6-Hydroxydopamine
NSC–233899 *see* Picloram
NSC–402815 *see* Penicillin G
NSC–403169 *see* Acronycine
NSC–409962 *see* BCNU
NSC–521778 *see* Hadacidin
NSC–525816 *see* Tenuazonic acid, sodium
NSC–526051 *see* α-Toluenesulfonic acid, α-anilino
NSC–529860 *see* Deaza-aminopterin
NSC–529861 *see* Chlorasquin
NSC–B116209 *see* OK-432
Nucleosides, as potential biologic markers in Burkitt's lymphoma, *59*:721

O

OK-432 (NSC–B116209)
clinical experience with the streptococcal anticancer preparation, *56*:211
tumor inhibitory effect of, in animal systems, *56*:9
Oncogenesis, and autoimmunity, *58*:441
Oncogenic viruses
inhibition of, DNA polymerase by tilorone and its analogs, *58*:821
interference with formation and expression of RNA tumor virus information: rationale and experimental results, *58*:579
molecular evidence for viral agents in human cancer and its chemotherapeutic consequences, *58*:595
Oncornaviruses, effect of streptonigrin and analogs on, replication and DNA polymerase activity, *57*:305
Orchiectomy, alone or plus estrogens for prostatic cancer, *58*:845
Osteogenic sarcoma *see* Sarcoma, osteogenic
Ovarian cancer *see* Carcinoma in man, ovary
2-Oxopropanal (NSC–79019)
arrest of cancer in mice by therapy with normal metabolites, *51*:455
indefinite survivors among mice treated with, *52*:687
Oxygen, effect of hyperbaric oxygen and mechlorethamine on Ehrlich ascites tumor, *52*:405
Oxygen inhalation, plus 5-FU therapy for large bowel cancer, *58*:951

P

P288 leukemia *see* Tumor systems in animals, leukemia, P288 lymphocytic
P388 leukemia *see* Tumor systems in animals, leukemia, P388 lymphoid
Pactomycin (NSC–52947), mechanism of action of, on protein synthesis, *58*:479
Pancreatic cancer *see* Carcinoma in man, pancreatic
PAP (prostatic acid phosphatase)
activity of cultured cells, *59*:59,147
design of spindle poisons activated specifically by, and new methods for cytochemistry, *59*:233
Papaverine (NSC–35443), unorthodox therapy for murine neuroblastoma with, *59*:571
PCA *see* 3(or 5)-Aminopyrazole-4-carboxamide
β-Peltatin (NSC–24819), inhibition of cilia regeneration and mitosis by, *56*:557
Penicillin G (NSC–402815), inhibitory effect of, in animal systems, *56*:9
Pharmacokinetics
analysis of the effects of antitumor drugs on cell cycle kinetics, *59*:847
considerations of resistance to anticancer drugs, *59*:795
cytokinetic aspects of clinical drug resistance, *59*:805
disposition of cytosine arabinoside and its metabolites: a pharmacokinetic simulation, *59*:861
human model for isophosphamide, *59*:877
kinetic model for the disposition and metabolism of moderate- and high-dose methotrexate in man, *59*:811
mathematic models for cancer chemotherapy: pharmacokinetic and cell kinetic considerations, *59*:827
preliminary model for adriamycin, *59*:819
some fundamental considerations of the applications of, to cancer chemotherapy, *59*:777
stochastic compartmental modeling of the disposition of DTIC, *59*:843
Phase I studies *see also* Clinical studies
adriamycin plus cyclophosphamide in patients with solid tumors, *58*:919
adriamycin plus 5-FU in the treatment of breast cancer and other solid tumors, *59*:1163
ammonium, trimethylpurin-6-yl chloride, in advanced cancer, *52*:417
5-azacytidine in patients with metastatic cancer, *58*:899
5-azacytidine in patients with solid tumors, *56*:413
5-azacytidine using a 24-hour continuous infusion for 5 days in the treatment of various cancers, *59*:1123
azotomycin plus 5-FU in colon carcinomas, *54*:109
bleomycin in the treatment of advanced cancer, *56*:197
butyraldehyde, 3-ethoxy-2-oxo-bis(thiosemicarbazone) in advanced cancer, *51*:171
camptothecin plasma levels in the treatment of advanced cancer, *56*:573
chromomycin A_3 in the treatment of advanced cancer, *57*:341
Corynebacterium parvum in the treatment of various solid tumors, *59*:1139
cyclocytidine for solid tumors and acute leukemias, *59*:389
cyclophosphamide plus adriamycin in patients with solid tumors, *58*:919
cytosine arabinoside in acute leukemia in children, *50*:287
2′-deoxy-5-(trifluoromethyl)uridine in the treatment of advanced cancer, *55*:205
dibromodulcitol in the treatment of advanced tumors, *55*:61

cis-dichlorodiammineplatinum(II) in solid tumors, *57*:459
cis-dichlorodiammineplatinum(II) plus various agents in the treatment of cancer, *58*:618
cis-dichlorodiammineplatinum(II), toxic effects of, *57*:465
2-(dimethylamino)-3′,4′-dihydroxyacetophenone hydrochloride in solid tumors, *52*:297
emetine in the treatment of epidermoid bronchogenic cancer, *59*:1171
evaluation of antibiotic drug A-649, *53*:71
evaluation of 6-azauridine in solid tumors, *53*:79
five-drug therapy for advanced breast cancer, *55*:183
guanazole in various tumors, *59*:1117
ICRF-159, clinical trial of, *58*:393
ICRF-159 in human solid tumors, *57*:185
inosine dialdehyde, *59*:1007
isophosphamide, *59*:751
6-mercaptopurine and 6-thioguanine plus azaserine for terminal chronic myelocytic leukemia, *58*:233
6-mercaptopurine in the treatment of advanced cancer, *51*:277
methyl-GAG administered im in various cancers, *58*:689
methyl methanesulfonate, clinical study, *50*:675
6α-methylpregn-4-ene-3,11,20-trione, clinical study of, *50*:671
mitoclomine in chronic lymphocytic leukemia, *59*:1173
pharmacologic study of 1-acetyl-2-picolinoylhydrazine, *53*:131
phenesterin in the treatment of advanced breast cancer, *55*:259
porfiromycin in advanced cancer, *51*:283,497
porfiromycin in large intermittent doses in advanced cancer, *56*:615
pseudourea in the treatment of metastatic cancer, *55*:91
streptozotocin, nephrotoxicity of, *54*:457
thalicarpine, a plant alkaloid, *59*:1001
tilorone in the treatment of advanced cancer, *57*:209
toyocamycin in the treatment of advanced cancer, *52*:301
VM-26 in the treatment of advanced cancer, *55*:575
VP-16-213, clinical trial of, in advanced cancer, *56*:769
VP-16-213, weekly administration of, *58*:901
weekly and daily treatment with camptothecin in advanced cancer, *56*:515

Phase II studies *see also* Clinical studies
A419, evaluation of, *53*:71
1-acetyl-2-picolinoylhydrazine in children with various malignant neoplasms, *59*:341
adriamycin in patients with metastatic melanoma, *59*:1181
adriamycin plus cyclophosphamide in patients with solid tumors, *58*:919
alanine mustard in advanced cancer, *54*:361
1-aminocyclopentanecarboxylic acid in patients with cancer, *54*:237
5-azacytidine in the treatment of advanced gastrointestinal cancer, *56*:649
azotomycin treatment in solid tumors, *52*:611
BCNU in advanced gastrointestinal cancer, *56*:267
BCNU in patients with solid tumors, *56*:787
BCNU in the treatment of bronchogenic carcinoma, *56*:259
BCNU in the treatment of Kaposi's sarcoma, *57*:325
BIC in primary and secondary brain tumors, *59*:327
BIC in the treatment of childhood malignancy, *59*:371
bleomycin in the treatment of Kaposi's sarcoma, *57*:325
bleomycin therapy for large bowel cancer, *56*:207
camptothecin in the treatment of advanced gastrointestinal cancer, *56*:94
carbestrol in patients with solid tumors, *56*:641
CCNU in the treatment of advanced gastrointestinal cancer, *58*:667
CCNU in the treatment of brain tumors, *56*:421
chlorambucil, effects of, in 374 patients with advanced cancer, *52*:661
chromomycin A_3 in advanced colorectal carcinoma, *59*:577
cyclophosphamide plus adriamycin in patients with solid tumors, *53*:919
cytembena in advanced colorectal carcinoma, *59*:581
cytosine arabinoside, BCNU, and prednisone for terminal chronic myelocytic leukemia, *58*:233
2′-deoxy-5-(trifluoromethyl)uridine in the treatment of advanced cancer, *55*:205
dibromodulcitol in the treatment of various cancers, *58*:653
cis-dichlorodiammineplatinum(II) and cyclophosphamide in the treatment of human malignancies, *59*:995
cis-dichlorodiammineplatinum(II) in advanced carcinoma of the large bowel, *57*:357
dihydroxybusulfan, clinical trials with, *52*:603
DTIC in the treatment of carcinoma of the lung, *55*:83
effects of patient selection on results of chemotherapy trials in gastrointestinal cancer, *58*:257
emetine in the treatment of epidermoid bronchogenic cancer, *59*:1171
emetine in the treatment of solid tumors, *57*:423
fluorometholone in advanced cancer, *51*:525
hexamethylmelamine for small cell carcinoma of the lung, *58*:371
hexestrol treatment in various cancers, *52*:751
hydroxyurea in malignant melanoma, *51*:503
ICRF-159 in advanced colorectal carcinoma, *59*:761
isophosphamide in patients with advanced breast cancer, *58*:861
6-mercaptopurine given intermittently in high doses, *54*:31
6-mercaptopurine in the treatment of advanced cancer, *51*:277
methyl-CCNU in the treatment of various solid carcinomas, sarcomas, and lymphomas, *59*:1021
6α-methylpregn-4-ene-3,11,20-trione in the treatment of solid tumors, *55*:265
meturedepa treatment in 233 patients with advanced cancer, *52*:667
mitoclomine in chronic lymphocytic leukemia, *59*:1173
procarbazine, streptozotocin, 6-thioguanine, or CCNU in patients with metastatic cancer of the large bowel, *59*:333
streptozotocin in the treatment of advanced gastrointestinal cancer, *55*:303

Phenester (NSC–116785), possible mediation of action by estrogen binding protein, *58*:353

Phenesterin (NSC–104469)
intestinal absorption of, an alkylating cholesterol compound, *56*:1
phase I study of, *55*:259
L-Phenylalanine mustard *see* Melphalan
Phosphine oxide, tris(2,2-dimethyl-1-aziridinyl) (NSC–118436), preparation and antitumor activity of, *51*:253
Phosphine sulfide, tris(1-aziridinyl)- *see* ThioTEPA
Phosphoramide mustard *see* Phosphorodiamidic acid, *N,N*-bis(2-chloroethyl)-, cyclohexylamine salt
Phosphorodiamidic acid, *N,N*-bis(2-chloroethyl)-, cyclohexylamine salt (NSC–69945)
clinical toxicology study of, *51*:35
pharmacologic studies of cyclophosphamide and its congener, *51*:335
primary evaluation of, in experimental antitumor assay systems, *50*:629
studies of some newer derivatives, *51*:347
Phosphoribosyl transferase, in colon tumor and normal mucosa as an aid in adjuvant chemotherapy with 5-FU, *58*:909
Picloram (NSC–233899), treatment of experimental mammary adenocarcinoma with, *58*:745
Pimelea simplex, antitumor activity of, *59*:585
Piposulfan (NSC–47774)
clinical experience with, *52*:275
effect of, on malignant lymphomas and solid tumors, *52*:433
treatment in chronic granulocytic leukemia, *53*:121
Platinum "blues"
antitumor activity of, in Sarcoma 180, *59*:589
platinum-pyrimidine blues, and related complexes, methods of synthesis, suggested classification scheme, and initial activity in animal tumors, *59*:287
platinum uracil blue, preliminary clinical studies with, *59*:647
platinum uracil blue, tissue distribution, antitumor activity in animals, and synthesis of, *59*:629
Platinum compounds
chemistry and biologic activity of, *59*:589
clinical studies of, in various malignant diseases, *59*:647
coordination complexes of, as antitumor agents, *59*:629
Podophyllotoxin (NSC–24818), attempts to demonstrate cytotoxic activity by specific activation by PAP, *59*:233
Poly IC (NSC–120949), effect of autoclaving on the molecular weight and chemotherapeutic activity of clinical samples of, *56*:31
Polyamines
potential biologic markers in Burkitt's lymphomas, *59*:721
urinary excretion of, in patients with advanced malignancy, *59*:1103
Polysaccharides, antitumor activity of, from *Flammulina velutipes* (Curt. ex Fr.) Sing., *57*:85
Porfiromycin (NSC–56410)
further clinical trial with, in large intermittent doses, *56*:615
in the treatment of disseminated squamous cancer of the cervix, *53*:305
phase I studies of, *51*:283
phase I trial of, in advanced cancer, *51*:497
Poricin (NSC–107455), immunodiffusion assay of, *56*:725
Prednisolone (NSC–9900), combined with 5-FU and methotrexate in the treatment of hepatoma, *59*:1167
Prednisone (NSC–10023)
combined with cyclophosphamide and vincristine in the treatment of diffuse non-Hodgkin's lymphoma, *59*:421
combined with cyclophosphamide with or without chloroquine in the treatment of multiple myeloma resistant to melphalan, *59*:557
combined with daunorubicin, cytosine arabinoside, and vincristine in the treatment of advanced adult acute leukemia, *59*:757
combined with daunorubicin, 6-thioguanine, cytosine arabinoside, and vincristine in the treatment of adults with acute nonlymphocytic leukemia, *59*:1131
combined with various agents in leukemia and lymphoma, *58*:521
combined with vinblastine in the treatment of acute monocytic leukemia in children, *59*:385
intermittent high-dose therapy for multiple myeloma, *51*:171
plus adriamycin in metastatic mammary carcinoma, *58*:251
plus L-asparaginase, causing ketotic hyperglycemia, *56*:781
plus BCNU and cytosine arabinoside in the treatment of terminal chronic myelocytic leukemia, *58*:233
plus cyclophosphamide, vincristine, and prednisone combination for acute leukemia in adults, *56*:543
plus cytosine arabinoside and vincristine, therapy for acute leukemia, *52*:305
plus daunorubicin and/or vincristine in advanced childhood acute lymphocytic leukemia, *56*:729
plus daunorubicin and vincristine for remission induction of childhood acute lymphocytic leukemia, *55*:79
plus 5-FU, methotrexate, vincristine, and cyclophosphamide for disseminated adenocarcinoma, *56*:761
plus hydroxyurea in the treatment of acute myelocytic leukemia, *55*:199
plus thiopurines in the treatment of acute childhood leukemia, *52*:321
remission induction in childhood leukemia with second course, plus vincristine, *54*:113
third and fourth remission induction with, plus vincristine in children with acute leukemia, *54*:293
treatment of metastatic carcinoma of the female breast with combination of, and other chemotherapy, *52*:743
Private practice of medical oncology, an analysis, *58*:759
Procarbazine (NSC–77213)
combined with actinomycin D and vinblastine in the treatment of malignant melanoma, *59*:767
evaluation of, in the treatment of acute leukemia, *57*:371
high-dose intermittent iv infusion of, *57*:361
in the treatment of advanced bronchogenic carcinoma, *53*:135
in the treatment of advanced Hodgkin's disease, *53*:39
in the treatment of multiple myeloma, *54*:245
phase II trials with, in patients with metastatic cancer of the large bowel, *59*:333
plus 5-FU in advanced carcinoma of the lung, *54*:369

response of childhood histiocytosis X to, *58*:719
response in male and female mice with Taper liver tumor, *53*:325
used in potential test systems in animals to determine activity against prostatic carcinoma, *59*:175
1-Propanol, 3,3′-iminodi-, dimethanesulfonate (ester), *p*-toluenesulfonate (NSC–140117)
a new methanesulfonic acid ester of aminoglycol, in the management of lung cancer, *59*:367
in the treatment of malignant lymphoma, *57*:159
Prostaglandins, oncolytic action of, *58*:503
Prostatic carcinoma *see* Carcinoma in man, prostatic
Protein synthesis, mechanisms of action of antitumor antibiotic inhibitors of, *58*:479
Pseudourea (NSC–56054)
effect of, on DNA, RNA, and protein synthesis in cultured cells, *57*:399
phase I and phototoxicity studies, *55*:91
photosensitization of, *55*:525
Pulmonary fibrosis, following multiple treatment with bleomycin in dogs, *58*:301
Pulmonary oil embolism, clinical and experimental studies of, *52*:81
Pyridoxal phosphate (NSC–82388), effect of, on toxicity and antitumor activity of mitomycin C and 4-deoxypyridoxine hydrochloride in rats, *50*:313
Pyrimidine catabolic end-products, as potential biologic markers in Burkitt's lymphoma, *59*:721

Q

Quinaspar (NSC–112846), dosage schedules in L1210 leukemia and toxicity, *55*:123
Quinazoline antifolates: biologic activities, *52*:697

R

R3230AC carcinoma *see* Tumor systems in animals, carcinoma
Radiation therapy
alone or in combination with various agents in the treatment of nonresectable cancer of the lung, *58*:359
altered sensitivity of hematopoietic stem cells to 5-FU following, *58*:813
combined with actinomycin D in the treatment of Wilms' tumor, *58*:5
combined with bleomycin, vincristine, and methotrexate in the treatment of non-oat-cell bronchogenic carcinoma, *59*:377
combined with chemotherapy: relevance of cell population kinetics and pharmacodynamics, *53*:313
combined with vincristine, cyclophosphamide, and actinomycin D in the treatment of childhood rhabdomyosarcoma, *59*:359
comparison of postoperative, alone and combined with BCNU in the management of malignant gliomas, *58*:841
development of immunity to L1210 leukemia in BDF_1 mice and effects of, *50*:55
extended-field, in prostatic carcinoma, *59*:165
increased clinically symptomatic pulmonary reactions with adjuvant chemotherapy, *58*:705
myocardial infarction as a possible complication of treatment with VP-16-213, mediastinal irradiation, or both, *59*:887
nitroheterocyclic drugs as selective radiosensitizers of hypoxic mammalian cells, *58*:559
plus 5-FU: an additive effect in bronchogenic carcinoma, *55*:253
plus 5-FU or iododeoxyuridine in bronchogenic carcinoma, *52*:263
plus hydroxyurea in the treatment of cervical carcinoma, *52*:601
plus methotrexate, treatment of advanced carcinoma of the head and neck, *56*:745
plus surgery and chemotherapy for patients with disseminated neuroblastoma, *56*:499
possible pericarditis in Hodgkin's disease, *54*:199
for prostatic cancer in man, *59*:251
reversion by testosterone of, induced hematologic depression in rats, *50*:649
role of radiation repair mechanism in, failures, *58*:527
sensitization by halopyrimidines (review), *58*:539
total-body, for disseminated lymphosarcoma (pilot study), *58*:401
Radiography, case for using only maximum diameter in measuring tumors, *50*:119
Rauscher leukemia virus *see* Oncogenic viruses
Rectal carcinoma *see* Carcinoma in man, rectal
Reserpine (NSC–59272), induced hypothermia, effect of, on lifespan in L1210 leukemia, *58*:317
Retinoblastoma
chemotherapeutic trials in patients with metastatic, *52*:631
cyclophosphamide in the treatment of children with, *51*:403
Rhabdomyosarcoma
combination therapy including vincristine for, *52*:489
cyclophosphamide treatment in, *51*:401
effect of vincristine on, *52*:497
embryonal, actinomycin D in the treatment of, *58*:49
embryonal, recurrent masses at sites of prior Krebiozin injections, *58*:249
in children, 1-acetyl-2-picolinoylhydrazine in the treatment of, *59*:341
in children, DTIC in the treatment of, *59*:351
in children, vincristine, actinomycin D, and cyclophosphamide, with or without radiation therapy in the treatment of, *59*:359
vincristine plus actinomycin D and cyclophosphamide in embryonal, *58*:281
Rhodium(II) acetate
inhibition of deamination of cytosine arabinoside by, *59*:661
interaction of, with molecules of biologic importance, *59*:611
Rhodium(II) butyrate, interaction of, with molecules of biologic importance, *59*:611
Rhodium(II) propionate, interaction of, with molecules of biologic importance, *59*:611
Ricin (NSC–9902), molecular pharmacology of, *58*:491

Ridgway osteogenic sarcoma *see* Tumor systems in animals, sarcoma, Ridgway osteogenic
RNA, molecular evidence for viral agents in human cancer and its chemotherapeutic consequences, *58*:595
RNA tumor viruses *see* Oncogenic viruses
Rubidazone (NSC–164011)
development of resistance to, in Ehrlich ascites tumor in vivo, *59*:301
toxicologic screening in rats, *59*:707

S

SAH 1-1 adenocarcinoma *see* Tumor systems in animals, adenocarcinoma
Sangivamycin (NSC–65346), initial toxicity study of, *51*:197
DL-*ortho*-Sarcolysin (NSC–57199)
in the treatment of multiple myeloma, *51*:517
in the treatment of solid tumors, *50*:685
L-Sarcolysin *see* Melphalan
Sarcoma
advanced, adriamycin alternating with vincristine plus actinomycin D in the treatment of, *59*:1035
1-aminocyclopentanecarboxylic acid in the treatment of, *54*:237
criteria for resection of, metastatic to the lung, *58*:285
cis-dichlorodiammineplatinum(II) plus cyclophosphamide in the treatment of, *59*:995
Ewing's
actinomycin D in the treatment of, *58*:49
cyclophosphamide in the treatment of children with, *51*:403
metastatic, evaluation of chemotherapy in children with, *55*:67
metastatic, treatment of, with actinomycin D, *54*:103
treatment of, with adriamycin, *56*:635
gynecologic, chemotherapy of, *51*:507
late-stage childhood, comparison of daunorubicin with adriamycin in, *58*:671
metastatic, vincristine plus DTIC plus adriamycin combination chemotherapy for, *58*:265
osteogenic
evaluation of chemotherapy in children with, *55*:67
evaluation of mitomycin C in the treatment of metastatic, *53*:297
high-dose methotrexate with citrovorum factor rescue in the treatment of metastatic bone tumors, *58*:275
hyperthermia as an adjuvant in the treatment of, *59*:257
melphalan administration in: an evaluation of dosage schedules, *55*:151
mitomycin C plus phenylalanine mustard and vincristine in the treatment of, *55*:189
pharmacokinetics of adriamycin in patients with, *58*:271
reticulum cell
BCNU in the treatment of advanced, *58*:383
recovery after inadvertent massive overdosage of vincristine, *55*:525
vinblastine plus vincristine given in intensive 3-day courses for, *57*:481
Sarcoma 180 *see* Tumor systems in animals, Sarcoma 180
Scandinavian Adjuvant Chemotherapy Group, preliminary report from, *55*:561
Schwannoma, combination therapy with vincristine and cyclophosphamide for generalized malignant, *54*:65
Serum albumin, effect of L-asparaginase on, in man, *53*:67
Sodium thiosulfate (NSC–45624), a nitrogen mustard antagonist, toxicity of, in the dog, *50*:255
Soviet Union, methods of screening anticancer drugs in, *54*:71
Sparsomycin (NSC–50729), mechanism of action of, on protein synthesis, *58*:479
SPG-827 (NSC–42076), clinical studies of, *50*:565
SPI-77 (NSC–72274), clinical studies of, *50*:565
Spindle poisons, activated specifically by PAP, as potential cytotoxic agents, *59*:233
Spleen colony formation
altered sensitivity of hematopoietic stem cells to 5-FU following endotoxin, cyclophosphamide, or irradiation, *58*:813
cell cycle specificity and therapeutic effectiveness of cytostatic agents, *56*:691
studies of L1210 leukemia; differential sensitivity of normal and leukemic bone marrow colony-forming cells to cytosine arabinoside therapy, *51*:423
studies of L1210 leukemia; differential sensitivities of normal hematopoietic and resistant cells to 6-mercaptopurine, *52*:251
studies of L1210 leukemia; growth kinetics of lymphocytic L1210 cells in vivo as determined by, assay, *51*:415
studies of L1210 leukemia; sensitivities of L1210 and L1210/6-MP to triazenoimidazole carboxamides, *52*:393
Squamous cell carcinoma *see* Carcinoma in man, squamous cell
Statistics in clinical trials
automated response—decisions in cancer chemotherapy trials, *57*:137
case for using only maximum diameter in measuring tumors, *50*:119
computer model for tumor growth and chemotherapy and its application to L1210 leukemia treated with cytosine arabinoside, *54*:399
effective consultation for clinical study groups, *53*:1
effect of chemotherapy on kinetics of leukemic cells, *50*:296
electronic computers for evaluation of clinical data; man versus machine, *50*:141
electronic computers for evaluation of clinical data; man versus man, *50*:151
electronic computers for evaluation of clinical data; interpretation of data, *50*:157
estimation of human body surface area from height and weight, *54*:225
evaluation of survival data and two new rank order statistics arising in its consideration, *50*:163
in vivo determination of the fractional kill of human tumor cells by chemotherapeutic agents, *56*:563
last surviving cancer cell: the chances of killing it, *50*:541
possible approaches to selective toxicity: new concepts in cancer chemotherapy, *51*:247

problems in evaluating tumor responses in the clinical drug evaluation program, *50*:113
survival rates of patients with prostatic cancer, tumor stage and differentiation, *50*:129
treatment for prostatic cancer using an exponential-type life model relating survival to concomitant information, *58*:845
what shall we measure on whom? why?, *50*:107
Stomach carcinoma *see* Carcinoma in man, stomach
Streptoccocal preparation *see* OK-432
Streptococcus faecalis, biologic activity of daunorubicin in, *52*:707
Streptonigrin (NSC–45383)
and analogs, effect of, on oncornavirus replication and DNA polymerase activity, *57*:305
comparison of biochemical effects of isopropylidine azastreptonigrin with, *51*:19
comparative teratogenic effects of, and derivatives, in the rat, *53*:23
evaluation of, by continuous iv infusion in the treatment of advanced gastrointestinal cancer, *51*:73
Streptonigrin methyl ester (NSC–45384), comparative teratogenic effects of streptonigrin and, in the rat, *53*:23
Streptozotocin (NSC–85998)
antileukemic activity of, and its analogs, *56*:709
fate of, in the treatment of patients with advanced cancer, *59*:547
in the treatment of lymphoreticular malignancies, *59*:443
metastatic renal adenocarcinoma produced by, *59*:891
nephrotoxicity of, *54*:457
new model for studying the effect of, in the growth of the prostate gland in rats, *59*:185
patterns of iv glucose tolerance and insulin response before and after, in patients with cancer, *56*:61
phase II study of, in the treatment of advanced gastrointestinal cancer, *55*:303
phase II trials with, in patients with metastatic cancer of the large bowel, *59*:333
renal tumorigenic action of, in rats, *52*:563
tissue distribution of, *58*:157
urinary excretion of β-glucuronidase after administration of, to Fischer rats, *57*:235
used in potential test systems in animals to determine activity against prostatic carcinoma, *59*:175
Streptozotocin analogs, antileukemic activity of, *56*:709
Strophanthin G (NSC–25485), lack of effect on cardiac uptake of adriamycin, *59*:765
Structure-activity studies
antitumor and immunosuppressive activities of lankacidin-group antibiotics, *59*:919
the role of, in the design of antitumor agents, *59*:679
Surgery
comparison of, plus irradiation alone and combined with BCNU in the management of malignant gliomas, *58*:841
criteria for resection of sarcoma metastatic to the lung, *58*:285
cure of metastatic Lewis lung carcinoma with methyl-CCNU and, plus chemotherapy, *56*:183
effect of resection of the primary neoplasm on responsiveness to chemotherapy of patients with large bowel cancer, *56*:551
methodologic aspects of cancer chemotherapy after radical surgery, *58*:129
plus adjuvant chemotherapy with nitromin and cyclophosphamide in stomach and bronchial carcinoma, *56*:35
plus BCNU in an animal brain tumor model, *58*:627
plus radiotherapy and chemotherapy for patients with disseminated neuroblastoma, *56*:499
relationship of dose schedules to the effectiveness of adjuvant therapy in Lewis lung tumor, *54*:379
Survival of cancer patients, what shall we measure on whom? why?, *50*:107

T

TA3Ha cells *see* Tumor systems in animals, mammary carcinoma
Taper liver tumor *see* Tumor systems in animals, Taper liver
Temperature, adjuvant effects in cancer therapy, *57*:373
Tenuazonic acid, *N,N'*-dibenzylethylene diamine (NSC–82260), cardiovascular and gastrointestinal effects of, *52*:587
Tenuazonic acid, sodium (NSC–525816), toxicity of, in animals, *52*:579
TEPA *see* Tris(2,2-dimethyl-1-aziridinyl)phosphine oxide
Tris(2,2-dimethyl-1-aziridinyl)phosphine oxide (NSC–9717), initial clinical study of, *56*:393
Teratogenesis
comparative effects of streptonigrin and its derivatives in the rat, *53*:23
effect of cyclophosphamide in the rat, *51*:363
Terephthalanilide, 2-amino-4',*A*"-bis(5-methyl-2-imidazolin-2-yl)- (NSC–66761), toxicity and physiologic distribution of, *50*:9
Testicular cancer *see* Carcinoma in man, testicular
Testosterone (NSC–9700)
as a lysosomal labilizer in the treatment of mammary gland carcinomas with cyclophosphamide, *50*:47
possible inhibitory effect of androgens on bone marrow suppression by cytotoxic agents—a dose-dependent phenomenon?, *58*:125
reversion by, of radiation-induced hematologic depression in rats, *50*:649
Testosterone enanthate (NSC–1759), effect of, on erythropoiesis in irradiated mice given marrow transfusions, *52*:627
Δ^1-Testololactone (NSC–23759)
comparison with Deluteval 2x in the treatment of metastatic breast cancer, *54*:249
massive doses of, for advanced breast cancer, *50*:323
Tetrahydrouridine (NSC–112907)
inhibition of deamination of cytosine arabinoside by, *59*:717
used to enhance the oral activity of 5-azacytidine in L1210 leukemic mice, *59*:459
Tetramisole (NSC–102063), effects of, in experimental tumor systems, *59*:697

Thalicarpine (NSC–68075), phase I study of, *59*:1001
Thallium chloride (NSC–15197), toxicity and antitumor activity in experimental rodent tumors, *59*:599
Therapeutic index, determination of, of drugs by in vitro sensitivity tests using human host and tumor cell suspensions, *57*:11
2-Thio-6-azauridine (NSC–146268), antitumor activity and mode of action of, on L1210 leukemia, *58*:345
1,3,4-Thiadiazole, 2,2′-(methylenediimino)bis- (NSC–143019), effects of, on tumor growth and immune responses in mice, *58*:331
6-Thioguanine (NSC–752)
combined with azaserine for multiple myeloma, *51*:234
combined with daunorubicin, cytosine arabinoside, prednisone, and vincristine, in the treatment of adults with acute nonlymphocytic leukemia, *59*:1131
development of a microbiologic assay capable of detecting cytosine arabinoside in body fluids in the presence of, *59*:515
disposition of, in solid L1210 leukemia tumor-bearing mice, *57*:275
phase II trials with, in patients with metastatic cancer of the large bowel, *59*:333
plus azaserine in the treatment of terminal chronic myelocytic leukemia, *58*:233
plus cytosine arabinoside, in cytosine arabinoside-sensitive and -resistant P815 mouse neoplasms, *57*:349
ThioTEPA (NSC–6396)
combined with other agents in the treatment of patients with advanced cancer, *52*:597
cytologic studies on human melanoma cells in tissue culture, *52*:543
equipment and techniques of continuous infusion of, in humans and animals, *51*:49
Tilorone (NSC–143969)
and its analogs, inhibition of Rauscher leukemia virus and avian myeloblastosis virus DNA polymerases by, *58*:821
phase I study of, a non-marrow depressing antitumor agent, *57*:209
α-Toluenesulfonic acid, α-anilino- (NSC–526051), inhibition of lactate dehydrogenase by, *50*:89
Toxic reactions: animals
antineoplastic and toxic effects of *Acinetobacter* and *Pseudomonas* glutaminase-asparaginases, *58*:829
cardiotoxicity of anthracycline antibiotics in rats, *59*:707
comparison of the acute hemolytic and cardiovascular actions of ellipticine and its analogs, *58*:637
effect of *p*-carboxycarbanilic acid, *N*-[*p*-[bis(2-chloroethyl)amino]phenyl] ester, *54*:23
effect of OK-432 in various animals, *56*:9
evaluation of sialogogic action of cyclocytidine and anhydro-ara-5-fluorocytidine, *59*:1019
hearing loss in rhesus monkeys treated with *cis*-dichlorodiammineplatinum(II), *59*:467
hemorrhagic encephalopathy induced by cyclophosphamide in suckling rats, *54*:211
inability of strophanthin G to affect cardiac uptake of adriamycin, *59*:765
nephrotoxic effects of cytembena in dogs and monkeys, *59*:1071
pathologic changes induced by daunorubicin in the Syrian golden hamster, *54*:15
pharmacologic effects of 1,2:5,6-dianhydrogalactitol, *56*:593
potential hazards associated with the use of 1-methyl-1-nitrosourea, *58*:617
prevention of hemolysis induced by ellipticine in rhesus monkeys, *58*:117
pulmonary fibrosis following multiple treatment with bleomycin in dogs, *58*:301
reversion by testosterone of radiation-induced hematologic depression in rats, *50*:649
studies with mitomalcin in dogs, *54*:217
teratogenic effects of cyclophosphamide in the rat, *51*:363
Toxic reactions: man *see* Adverse reactions
Toyocamycin (NSC–63701), phase I study of, *52*:301
Triazenoimidazoles, quantitative structure-activity relationships of, in the treatment of L1210 leukemia, *56*:443
Triazinate (NSC–139105), an antifolate drug, preclinical studies with, in beagle dogs and rhesus monkeys, *59*:523
Triethylene melamine (NSC–9706), response in male and female mice with Taper liver tumor, *53*:325
Triethylenephosphoramide *see* ThioTEPA
Trimethylcolchicinic acid, methyl ether (NSC–36354)
clinical trial of, in advanced cancer, *51*:25
further study of, in patients with malignant melanoma, *56*:253
Trimethyl-6-ylammonium chloride *see* Ammonium, trimethylpurine-6-yl-chloride (NSC–51095)
Triton WR–1339 (NSC–90255), further studies on selective cytotoxicity of, *52*:243
Tryptophan mustard (NSC–62403), in the treatment of acute leukemia and malignant solid tumors in children, *52*:445
Tumor cell kill, estimation of, from Gompertz growth curves, *59*:267
Tumor scanning, failure with Indium 111-labeled bleomycin to predict response to bleomycin treatment, *58*:733
Tumor systems in animals
adenocarcinoma
MAC-13 and MAC-15, chemotherapy of, with various agents, *59*:1083
SAH 1-1, influence of anatomic location on susceptibility to chemotherapy, *53*:105
TA3Ha mammary, in culture, effects of macromycin on, *58*:181
ADJ/PC6A tumor, antitumor activity of platinum-pyrimidine blues and related complexes against, *59*:287
adriamycin: a new antibiotic with antitumor activity against, *53*:33
antitumor activity of a homo-aza-steroidal ester of [*p*-[bis(2-chloroethyl)amino]phenyl]acetic acid against, *57*:365
antitumor activity of 5-amino-4-imidazolethiocarboxamide derivatives on a variety of, *53*:165
antitumor activity of 5-formamido-1-β-D-ribofuranosylthioimidazole-4-carboxamide 2′,3′,5′-triformate against, *55*:229
antitumor activity of 1-methyl-1-nitrosourea against, *58*:135

antitumor and other biologic properties of L-asparaginase against, *52*:617
arrest of cancer in mice by therapy with normal metabolites; indefinite survivors among mice treated with mixtures of 2-oxopropanal and 2,3-dihydroxypropanal, *52*:687
biologic activity of some adriamycin derivatives against, *58*:769
brain
effectiveness of the nitrosoureas as a function of their lipid solubility in, *58*:707
effect of CCNU in sesame oil administered im in the treatment of, *56*:457
effect of combined surgery and BCNU on, *58*:627
review of selected experimental models used in chemotherapy experiments, *59*:729
carcinoma
755
kinetic parameters and "cell cure" of moderately advanced, *53*:169
lack of effect of warfarin alone or in combination with 5-FU on primary and metastatic, *55*:29
Ehrlich ascites
anticancer activity of alkylating agents derived from various diamines and diols, *51*:205
antitumor activity of platinum-pyrimidine blues and related complexes against, *59*:287
antitumor activity of selected amino acid derivatives against, *59*:309
antitumor activity of withaferin A, *51*:271
cross resistance between vinca alkaloids and anthracyclines in, in vivo, *56*:701
development of resistance to adriamycin in, *56*:321
development of resistance to daunorubicin in, *55*:133
development of resistance to rubidazone in, *59*:301
effect of 2,2′-anhydro-1-(β-D-arabinofuranosyl)-cytosine hydrochloride and derivatives on, *58*:479
effect of hyperbaric oxygen and mechlorethamine on, *52*:405
effect of some drugs on, dissemination and metastases, *54*:79
interaction of rhodium(II) carboxylates with molecules of biologic importance, *59*:611
6-mercaptopurine combined with 6-methylmercaptopurine ribonucleoside in the therapy of, *51*:101
Krebs 2
combined action of deuterium oxide and chemotherapy on, *50*:641
cytopathologic effects of mercenene on, *50*:655
Lewis lung
antitumor activity of amygdalin MF (laetrile) alone and combined with β-glucosidase, *59*:951
continuous and limited courses of cyclophosphamide with pulmonary metastasis after surgery for, *51*:439
cure of metastatic, with methyl-CCNU and surgery-chemotherapy, *56*:183
differential sensitivity of colony-forming cells of, to BCNU, CCNU, and methyl-CCNU, *59*:929
effect of route of administration of mimosine on, *57*:41
effects of levamisole and tetramisole in, *59*:697
relationship of dose schedules to the effectiveness of adjuvant therapy, *54*:379
R3230AC of the rat, treatment of in vivo, with estradiol mustard and its molecular components, *57*:353
carcinosarcoma, effect of cyclophosphamide and its metabolites on, *51*:315
chemotherapeutic effects of compound 593A on, *57*:21
3-*N*,*N*-bis(2-chloroethylamino)*p*-toluic acid, a new cytostatic drug, active in, *54*:319
comparative effects of dibromodulcitol and dibromomannitol, *53*:377
effectiveness of daunorubicin against, *50*:659
effect of L-asparaginase on transplantable and solid tumors from mice and rats, *53*:189
effect of *p*-carboxycarbanilic acid, *N*-[*p*-[bis(2-chloroethyl)amino]phenyl] ester in, *54*:23
effect of cholesterol-free, fat-free diet, and hypocholesteremic agents on transplantable, *50*:25
effect of 1,3,4-thiadiazole, 2,2′-(methylenediimino)bis-on, *58*:331
effect of vitamin A on transplantable and chemically induced tumors, *55*:53
effects of glutaminase-asparaginases in, *58*:829
evaluation of actinomycins in experimental systems, *58*:63
evaluation of 4-carbethoxy-5-(3,3-dimethyl-1-triazeno)-2-phenylimidazole and 4-carbethoxy-5-(3,3-dimethyl-1-triazeno)-2-methylimidazole as potential antitumor agents, *57*:263
experimental screening procedures and clinical predictability value (review), *50*:173
fibrosarcoma
KHT, activity of concanavalin A on, *59*:319
MCAM-7 (3-methylcholanthrene-induced), specificity of cell membrane antigens in, *59*:127
Glioma 26, relationship of lipophilicity of imidazole carboxamides to activity against, *59*:327
hepatoma
AH13, AH60C, and AH7974, antitumor activity of selected amino acid derivatives against, *59*:309
effect of pyridoxal phosphate on activity of mitomycin C and 4-deoxypyridoxine hydrochloride, *50*:313
Morris chemotherapy of: correlation of size and weight of tumor and preliminary data with 5-fluorodeoxyuridine, *57*:245
human prostatic tumors in mice, *59*:47
hyperthermia in the treatment of, *58*:294
inhibitory effect of 2-mercapto-3-hydroxypropanal on transplantable cancer in mice, *53*:195
intrathecal injection of methotrexate in transplanted brain tumors, *51*:1
kinetic parameters and growth curves for, *54*:143
leukemia
AKR
basic and therapeutic trial results obtained in the spontaneous AKR model—end of 1971 (review), *56*:273

increased immunogenicity of, by 3(or 5)-aminopyrazole-4-carboxamide, *57*:3
relationship between white blood cell count and diagnosis and therapeutic response in AKR mice with spontaneous, *56*:683
response to therapy of spontaneous, first passage, and long passage lines of, *53*:345
spontaneous, as a model system, *53*:329
chemotherapy of (review), *55*:309
continuing long-term remission after cyclophosphamide therapy in dogs, *53*:223
cytotoxicity of BIC on, *55*:43
Dunning ascites
inhibition of, with *cis*-dichlorodiammineplatinum(II), *55*:235
studies of some newer phosphoramide mustards on, *51*:347
L1210
activity of anhydro-ara-C compared with cytosine arabinoside with respect to treatment schedule dependency, *56*:483
antileukemic action of a new sugar derivative dimethanesulfonate and related compounds, *53*:367
antileukemic activity of streptozotocin and its analogs in, *56*:709
antitumor activity and mode of action of 2-thio-6-azauridine on, *58*:345
antitumor activity of amygdalin MF (laetrile) as a single agent and combined with β-glucosidase, *59*:939
antitumor activity of platinum-pyrimidine blues and related complexes against, *59*:287
antitumor activity of selected amino acid derivatives against, *59*:309
antitumor activity of some acylhydrazines in, *58*:803
antitumor and immunosuppressive activities of lankacidin-group antibiotics against, *59*:919
antitumor effects of the antispermatogenic agent, 2,3-dihydro-2-(1-naphthyl)-4(1*H*)-quinazolinone, *56*:163
azotomycin: biologic fate in, *55*:47
biochemical, cytokinetic, pharmacologic, and toxicologic relationships of optimal therapeutic schedules, *54*:431
cancer chemotherapy in, metastatic to the lymph nodes, *54*:311
cell-mediated response to, subline antigenically altered following drug treatment in vivo, *58*:325
chemotherapeutic activity of daunorubicin and its isolated metabolites in, *56*:315
chemotherapeutic effects of compound 593A on, *57*:21
combination therapy with L-asparaginase and other agents, *54*:329
combined therapy with cytosine arabinoside and BCNU, *53*:215
comparison of antileukemic effect of adriamycin with daunorubicin, *54*:1
computer model for tumor growth and chemotherapy and its application to, treated with cytosine arabinoside, *54*:399
cytosine arabinoside in combination with 6-mercaptopurine, methotrexate, or 5-FU in, *51*:435
development of immunity to, in BDF_1 mice and effects of therapy, *50*:55
cis-dichlorodiammineplatinum(II) alone or combined with various other agents in the treatment of, *59*:629
differential sensitivities of normal and leukemic bone marrow colony-forming cells to cytosine arabinoside, *51*:423
disposition of cytosine arabinoside and 6-thioguanine in solid L1210 leukemia tumor-bearing mice, *57*:275
drug-tumor sensitivity matching procedure using diffusion chambers in vivo, *58*:189
effect of (α*S*,4*S*,5*R*)-α-amino-3-chloro-4-hydroxy-4,5-dihydro-5-isoxazoleacetic acid against, *58*:935
effect of 2,2′-anhydro-1-(β-D-arabinofuranosyl)-cytosine hydrochloride and derivatives on, *58*:451
effect of BCNU and cyclophosphamide on NAD glycohydrolase in, *52*:569
effect of BCNU and mechlorethamine on kinetic behavior of cultured, *51*:7
effect of CCNU and its degradation products on progression of, cells through the cell cycle, *55*:215
effect of day of dosage omission on survival time in the regularly scheduled methotrexate treatment of, *56*:25
effect of different doses of methotrexate, cytosine arabinoside, and cyclophosphamide on drug resistance in mice with, *56*:473
effect of reserpine-induced hypothermia on lifespan in, *58*:317
effect of route of administration of mimosine on, *57*:41
effectiveness of antileukemic agents in mice inoculated with, resistant to BIC, *53*:229
effectiveness of daunorubicin against, *50*:659
effects of levamisole and tetramisole in, *59*:697
enhancement by tetrahydrouridine of the oral activity of 5-azacytidine in, *59*:459
enhancement of the effectiveness of daunorubicin or adriamycin against, with ICRF-159, *59*:689
growth kinetics of lymphocytic, in vivo, as determined by spleen colony assay, *51*:415
growth of colonies of, in vitro, *51*:451
growth requirements and biologic characteristics of, in cell culture, *50*:247
increased immunogenicity of, by 3(or 5)-amino pyrazole-4-carboxamide, *57*:3
increased lifespan using the priming dose schedule design in carbazilquinone treatment of, *56*:19
in culture, effects of macromycin on, *58*:181
influence of mitotic cycle inhibitors on the antileukemic activity of cytosine arabinoside in mice bearing, *55*:547
influence of route of administration on antileukemic activity of cytosine arabinoside in advanced, in mice, *52*:399
influence of the stage of advancement of, in mice,

on the optimal schedule of treatment of cytosine arabinoside, *56*:327
inhibitory effect of 2-mercapto-3-hydroxypropanal, *53*:195
investigations with cyclophosphamide (review), *52*:359
kinetics of the effect of DTIC and BIC on the reproductive integrity of cultured, *52*:725
kinetics of the reduction in viability of cultured, exposed to 5-azacytidine, *56*:585
lack of effect of warfarin alone or in combination with 5-FU on primary and metastatic, *55*:29
6-mercaptopurine in combination with 6-methylmercaptopurine in chemotherapy of, *51*:111
modification of transplantability and tumor growth following treatment of, with macromycin, *57*:501
neocarzinostatin: an antitumor antibiotic effective against ascitic, *50*:79
new technique for the measurement of ascites cell numbers, *58*:741
on screening procedures, *54*:294
preliminary evaluation of (αS,5*S*)-α-amino-3-chloro-4,5-dihydroxy-5-isoxazoleacetic acid against, *57*:141
preliminary observations on temperature-enhanced drug uptake by leukemic leukocytes, in vitro, *59*:985
proposed new derivative of cytosine arabinoside to circumvent resistance, *58*:298
protection with *N*-acetyl-L-cysteine against isophosphamide toxicity and enhancement of therapeutic effect in, *57*:299
quantitative structure-activity relationships of nitrosoureas and triazenoimidazoles, *56*:443
quinazoline antifolates: biologic activities, *52*:697
quinazoline antifolates in the treatment of, *55*:123
scheduling of cytosine arabinoside to take advantage of its S-phase specificity against, *51*:125
sequential chemotherapy with cyclophosphamide and cytosine arabinoside in mice with advanced, *53*:265
solid lymphocytic, comparative distribution studies with cyclocytidine and cytosine arabinoside in, *59*:501
some determinants of the therapeutic efficacy of actinomycin D, adriamycin, and daunorubicin, *58*:55
spleen colony studies of, differential sensitivities of normal hematopoietic and resistant colony-forming cells to 6-mercaptopurine, *52*:251
spleen colony studies of, sensitivities of, and L1210/6-MP to triazenoimidazolecarboxamides, *52*:393
studies of some newer phosphoramide mustards on, *51*:347
treatment with carminomycin, *58*:255
treatment with water insoluble BIC and its water-soluble hydrochloride, *57*:383
tumor cell death in vivo after administration of chemotherapeutic agents, *53*:273
use of first generation transplants of a slow growing solid tumor for the evaluation of new cancer chemotherapeutic agents, *55*:233
value of cytosine arabinoside plus DTIC therapy in advanced, and enhancement of the combination with sequential doses of methotrexate and BCNU, *57*:291
variants resistant to DTIC and BIC, effectiveness of antileukemic agents in mice inoculated with, *55*:9
L4946, combined action of deuterium oxide and chemotherapy on, *50*:641
L5178Y
combination therapy with L-asparaginase and other agents, *54*:329
induction and characteristics of resistance to L-asparaginase in, *55*:115
MCDV-12 (Rauscher), antitumor activity of platinum-pyrimidine blues and related complexes against, *59*:287
P288 lymphocytic, some determinants of the therapeutic efficacy of actinomycin D, adriamycin, and daunorubicin, *58*:55
P388 lymphoid
antitumor activity of amygdalin MF (laetrile) alone and combined with β-glucosidase, *59*:951
antitumor activity of amygdalin MF (laetrile) as a single agent and combined with β-glucosidase, *59*:939
antitumor activity of *Pimelea simplex* against, *59*:585
chemotherapeutic activity of daunorubicin and its isolated metabolites in, *56*:315
comparison of antileukemic effect of adriamycin with daunorubicin, *54*:1
effects of levamisole and tetramisole in, *59*:697
SR61, antitumor activity of selected amino acid derivatives against, *59*:309
lung, Madison 109, effects of levamisole and tetramisole in, *59*:697
lymphoma
AKR, activity of concanavalin A on, *59*:319
failure of 5-carbamyl-L-cysteine plus L-asparaginase for L-asparaginase-resistant mouse, *56*:339
LAF-17 (radiation-induced), inhibition of antilymphoma allograft response in, by cyclophosphamide and isophosphamide, *59*:967
L5MF-22 (radiation-induced), inhibition of antilymphoma allograft response in, by cyclophosphamide and isophosphamide, *59*:967
lymphosarcoma, 6C3HED/OG, antitumor and immunosuppressive activities of lankacidin-group antibiotics on, *59*:919
mammary
action of prostaglandins on, *58*:503
drug-tumor sensitivity matching procedure using diffusion chambers in vivo, *58*:189
mammary carcinoma
activity of adriamycin and daunorubicin against, *56*:153
adenocarcinoma, treatment of experimental, with herbicides, *58*:745
chemotherapy of a spontaneous, in mice: relation between in vitro-in vivo activity and blood and

tumor concentrations of several antitumor agents, *57*:115
combinations of uracil mustard plus 3-ethoxy-2-oxo-, bis(thiosemicarbazone) in, *50*:557
modification of transplantability and tumor growth following treatment of TA3Ha cells with macromycin, *57*:501
role of lysosomal labilizers in the treatment of, with cyclophosphamide, *50*:47
spontaneous murine: model system for evaluation of combined methods of therapy, *55*:239
use of first generation transplants of a slow growing solid tumor for the evaluation of new cancer chemotherapeutic agents, *55*:233
melanoma
B16
antitumor activity of amygdalin MF (laetrile) as a single agent and combined with β-glucosidase, *59*:939
differential sensitivity of colony-forming cells of, to BCNU, CCNU, and methyl-CCNU, *59*:929
effects of levamisole and tetramisole in, *59*:697
effect of poly IC on, *56*:31
methods of screening anticancer drugs in the Soviet Union, *54*:71
mitogillin in the treatment of naturally occurring canine neoplasms, *55*:101
neuroblastoma
C1300, further evaluation of, with various antitumor agents, *59*:975
model of human disease, *57*:405
unorthodox therapy for, with 6-hydroxydopamine, bretylium tosylate, papaverine, and butyric acid, *59*:571
2-oxopropanal in the arrest of cancer systems in mice, *41*:455
P815, studies on drug resistance: combination chemotherapy with cytosine arabinoside plus 6-thioguanine in cytosine arabinoside-sensitive and -resistant, *57*:349
pharmacologic and antitumor effects of 1,2,:5,6-dianhydrogalactitol, *56*:593
phosphine oxide, tris(2,2-dimethyl-1-aziridinyl), antitumor activity of, *51*:253
plasmacytoma
altered sensitivity of a hamster, to cytosine arabinoside, *54*:337
effects of cyclophosphamide on primary and metastatic, in the hamster, *52*:345
primary evaluation of phosphordiamidic acid, *N,N*-bis(2-chloroethyl)-, cyclohexylamine salt in, *50*:629
prevention of cyclophosphamide immunosuppression by BCG, *58*:931
pulmonary metastasis, continuous and limited courses of cyclophosphamide in mice with, after surgery, *51*:439
sarcoma
180
activity of some derivatives of daunorubicin in, *57*:269
antitumor activity of platinum blue complexes against, *59*:589
antitumor activity of platinum-pyrimidine blues and related complexes against, *59*:287
antitumor activity of selected amino acid derivatives against, *59*:309
antitumor activity of some acylhydrazines in, *58*:803
antitumor activity of withaferin A, *51*:271
combined therapy with cytosine arabinoside and BCNU, *53*:215
developing need for perspective in surveys of antitumor test data, *54*:299
effects of some drugs on, dissemination and metastasis, *54*:79
metabolism of DTIC in, *56*:465
on screening procedures, *54*:294
Black, antitumor activity of withaferin A, *51*:271
chemotherapeutic response of, produced by murine sarcoma virus-transformed BALB/3T3 cells, *57*:149
E0771, antitumor activity of withaferin A, *51*:271
effectiveness of the nitrosoureas as a function of their lipid solubility in, *58*:787
lymphosarcoma, combination of uracil mustard plus 3-ethoxy-2-oxo-, bis(thiosemicarbazone) in, *50*:557
Moloney, virus-induced rhabdomyosarcoma, effects of levamisole and tetramisole in, *59*:697
Nakahara-Fukuoka, antitumor activity of selected amino acid derivatives against, *59*:309
Ridgway osteogenic
activity of actinomycin D against, *58*:55
antitumor activity of amygdalin MF (laetrile) alone and in combination with β-glucosidase, *59*:951
7-substituted actinomycin D analogs tested against, *58*:35
Yoshida
antitumor activity of selected amino acid derivatives against, *59*:309
effect of cyclophosphamide and its metabolites on, *51*:315
metastatic to lymph nodes, cancer chemotherapy screening with, *54*:311
studies of activity of polysaccharides from *Flammulina velutipes* (Curt. ex Fr.) Sing., *57*:85
SV40-transformed prostatic tumors in, establishment of tissue cultures from, *59*:51
Taper liver tumor, antitumor response to cancerostatic agents in male and female rodents, *53*:325
tumor inhibitory effect of OK-432, *56*:9
V × 2 carcinoma, combination therapy in isolation perfusion: use of mitotic inhibitors in pretreatment of, with alkylating agents, *56*:175
Walker 256 carcinosarcoma
antitumor activity of amygdalin MF (laetrile) as a single agent and combined with β-glucosidase, *59*:939
antitumor activity of gallium nitrate and other group IIIa metal salts in, *59*:599
antitumor activity of some acylhydrazines in, *58*:803
combinations of uracil mustard plus 3-ethoxy-2-oxo-, bis(thiosemicarbazone) in, *50*:557
effect of *p*-carboxycarbanilic acid *N*-[*p*-[bis(2-chloroethyl)amino]phenyl] ester in, *54*:23
effect of route of administration of mimosine on, *57*:41

experimental screening procedures and clinical predictability value (review), *50*:173
inhibition of, with *cis*-dichlorodiammineplatinum(II), *55*:235
oral activity of mitomycin C on, intramuscular, *52*:389
poricin in the treatment of an immunodiffusion assay of, *56*:725
studies on therapeutic effectiveness of drugs with tumor weight and survival time indices of, *52*:229

U

UC–51 (NSC–170898), activity against human tumor xenografts in immune-deprived mice, *58*:645
Uracil mustard (NSC–34462)
activity of combinations of, plus butyraldehyde, 3-ethoxy-2-oxo-, bis(thiosemicarbazone), against murine tumors, *50*:557
therapy for children with metastatic neuroblastoma, *52*:287
therapy in uncommon malignant neoplasms in children, *52*:441
treatment in metastatic retinoblastoma, *52*:631
Uterine cancer *see* Carcinoma in man, uterine

V

V × 2 Carcinoma *see* Tumor systems in animals, V × 2 carcinoma
Vaginal smear, nonhormonal cancer chemotherapy and, *51*:231
Vinblastine (NSC–49842)
alone or with mechlorethamine in pretreatment of V × 2 carcinoma undergoing isolation perfusion, *56*:175
arterial infusion of, in patients with solid tumors, *50*:573
biochemical studies with, *52*:463
chemotherapeutic response of human glial tumor cells cultured in cerebrospinal fluid, *51*:201
combined with continuous iv bleomycin in stage III testicular neoplasia, *59*:563
combined with procarbazine and actinomycin D in the treatment of malignant melanoma, *59*:767
cross resistance between vinca alkaloids and anthracyclines in Ehrlich ascites tumor in vitro, *56*:701
evaluation in the C1300 murine neuroblastoma model, *59*:975
historical background of vinca alkaloid research and areas of future interest, *52*:455
inhibition of cilia regeneration and mitosis by, *56*:557
in the treatment of advanced Hodgkin's disease, *53*:39
in the treatment of bronchogenic carcinoma, *55*:451
modification in biochemical pathways produced by, *52*:501
plus bleomycin therapy for disseminated testicular tumors, *58*:213
plus vincristine, clinical trial of weekly doses of, in malignant lymphoma and other neoplasms, *57*:477
plus vincristine, given in intensive 3-day courses as therapy for lymphomas, sarcomas, and other neoplasms, *57*:481
severe tumor pain with iv injection of, *50*:281
short-term sequential therapy with, and cyclophosphamide in Hodgkin's disease, *55*:607
vocal cord paralysis: a toxic reaction to, *55*:591
with or without prednisone in the treatment of acute monocytic leukemia in children, *59*:385
Vinca alkaloids
biochemical studies with, *52*:463
historical background of, research and areas of future interest, *52*:455
modifications in biochemical pathways produced by, *52*:501
Vincristine (NSC–67574)
clinical experience with, in tumors of the central nervous system and other malignant diseases, *52*:733
combination therapy including, for malignant solid tumors in children, *52*:489
combination therapy with cyclophosphamide and 5-FU, *52*:593
combined with actinomycin D and alternating with adriamycin in the treatment of advanced sarcomas, *59*:1035
combined with actinomycin D and cyclophosphamide with or without radiation therapy in the treatment of childhood rhabdomyosarcoma, *59*:359
combined with bleomycin and methotrexate plus radiation therapy in the treatment of non-oat-cell bronchogenic carcinoma, *59*:377
combined with cyclophosphamide and methyl-CCNU in the treatment of small cell carcinoma of the lung in a 3-week schedule, *59*:1127
combined with cyclophosphamide and prednisone in the treatment of diffuse non-Hodgkin's lymphoma, *59*:421
combined with daunorubicin, cytosine arabinoside, and prednisone in the treatment of advanced adult acute leukemia, *59*:757
combined with daunorubicin, 6-thioguanine, cytosine arabinoside, and prednisone in the treatment of adults with acute nonlymphocytic leukemia, *59*:1131
combined with DTIC in a comparative study with cyclophosphamide plus methyl-CCNU in patients with disseminated malignant melanoma, *59*:451
combined with 5-FU with or without cyclophosphamide in the treatment of various adenocarcinomas, *59*:425
combined with hydroxyurea in the treatment of metastatic renal cancer, *59*:1159
cross resistance between vinca alkaloids and anthracyclines in Ehrlich ascites tumor in vivo, *56*:701
effectiveness of, against refractory leukemia in children, *52*:473
effect of, on malignant solid tumors in children, *52*:497
evaluation in the C1300 murine neuroblastoma model, *59*:975
historical background of vinca alkaloid research and areas of future interest, *52*:455
in the treatment of children with acute leukemia, *52*:469
low doses of, for malignant disease, *53*:249
modification in biochemical pathways produced by, *52*:501

neurophysiologic alterations induced by, *52*:519
new model for studying the effect of, on the growth of the prostate gland in rats, *59*:185
orthostatic hypotension during combination chemotherapy with vincristine, *58*:927
physical activity: a possible determinant of vincristine neuropathy (when administered with 5-FU and cyclophosphamide), *58*:413
plus actinomycin D and cyclophosphamide for embryonal rhabdomyosarcoma, *58*:281
plus adriamycin and cyclophosphamide in the treatment of metastatic neuroblastoma, *56*:365
plus adriamycin in metastatic mammary carcinoma, *58*:251
plus BCNU in disseminated gastrointestinal cancer and other neoplasms, *58*:947
plus bleomycin in patients with lung cancer and other malignant tumors, kinetic scheduling of, *57*:219
plus cyclophosphamide, cytosine arabinoside, and prednisone combination for acute leukemia in adults, *56*:543
plus cyclophosphamide for generalized malignant schwannoma, *54*:65
plus cyclophosphamide in a cyclic program in the treatment of neuroblastoma in children, *51*:411
plus cyclophosphamide in neuroblastoma, *58*:683
plus cytosine arabinoside and prednisone, therapy for acute leukemia in adults, *52*:305
plus daunorubicin and prednisone for remission induction of childhood acute lymphocytic leukemia, *55*:79
plus daunorubicin and prednisone in advanced childhood acute lymphocytic leukemia, *56*:729
plus DTIC and adriamycin in the treatment of metastatic sarcoma, *58*:265
plus DTIC and cyclophosphamide, treatment of metastatic malignant melanoma with, *56*:357
plus 5-FU, DTIC, and BCNU given concomitantly in the treatment of solid tumors in man, *56*:107
plus 5-FU, methotrexate, cyclophosphamide, and prednisone for disseminated adenocarcinoma, *56*:761
plus mitomycin C and phenylalanine mustard in the treatment of osteogenic sarcoma, *55*:189
plus surgery, radiotherapy, cyclophosphamide, and daunorubicin for patients with disseminated neuroblastoma, *56*:499
plus vinblastine, clinical trial of weekly doses of, in malignant lymphoma and other neoplasms, *57*:477
plus vinblastine, given in intensive 3-day courses as therapy for lymphomas, sarcomas, and other neoplasms, *57*:481
recovery after inadvertent massive overdosage of, *55*:255
remission induction in childhood leukemia with second course, plus prednisone, *54*:113
response of acute leukemia in children to repeated courses of, *51*:465
response to spontaneous, first passage, and long passage lines of AKR leukemia, *53*:345
symposium, summary and prospectives, *52*:527
therapy for acute leukemia in children, *52*:477
therapy for malignant solid tumors in children (except Wilms' tumor), *52*:485
therapy for Wilms' tumor, *52*:481
third and fourth remission induction with prednisone plus, in children with acute leukemia, *54*:293
treatment in metastatic retinoblastoma, *52*:631
treatment of MAC-13 and MAC-15 adenocarcinomas of the colon in mice, *59*:1083
ultrastructural studies on tissue culture cells treated with, *52*:509
used in potential test systems in animals to determine activity against prostatic carcinoma, *59*:175
Vinleurosine sulfate (NSC–90636), clinical trial of, a new drug derived from *Vinca rosea* Linn., *50*:95
Viruses, role in prostatic cancer, *59*:17,33,39
Vitamin A, as a lysosomal labilizer in the treatment of mammary gland carcinomas with cyclophosphamide, *50*:47
Vitamin A acid (NSC–122758)
effects of, on transplantable and chemically induced tumors, *55*:53
therapy of actinic keratoses and basal cell carcinomas with local application of, *55*:59
VM–26 (NSC–122819)
clinical investigation of, in patients with malignant lymphomas and solid tumors, *56*:71
clinical studies with, *55*:575
compared to VP-16-213 in childhood cancer: preliminary observations, *59*:743
delayed toxicity of, in mice, *57*:165
VP–16–213 (NSC–141540)
clinical antitumor and toxicity study in solid tumors, *59*:737
compared to VM-26 in childhood cancer: preliminary observations, *59*:743
given orally to patients with advanced neoplastic disease, *59*:1027
myocardial infarction as a possible complication of treatment with, or mediastinal irradiation, or both, *59*:887
phase I clinical trial of, *56*:769
phase I clinical trial of weekly administration of, *58*:901

W

Walker 256 carcinosarcoma *see* Tumor systems in animals, Walker 256 carcinosarcoma
Warfarin (NSC–59813), lack of effect of, alone or in combination with 5-FU on primary and metastatic L1210 leukemia and adenocarcinoma, *55*:29
White blood cell count, relationship between, and diagnosis and therapeutic response in AKR mice with spontaneous leukemia (lymphoma), *56*:683
Wilms' tumor
actinomycin D in the treatment of, *58*:5,49
cyclophosphamide treatment in, *51*:407
pulmonary cysts—a complication in combined chemotherapy for, *50*:319
vincristine therapy for, *52*:481
Withaferin A (NSC–101088), antitumor activity of, *51*:271

X

Xenografts, activity against human tumor, in immune-deprived mice, *58*:645

Y

Yoshida sarcoma *see* **Tumor systems in animals, sarcoma, Yoshida**

Subject Index

A

Actinomycin D (NSC-3053)
and γ-radiation therapy against the Ridgway osteogenic sarcoma, *5(1)*:225
combination chemotherapy in a model breast tumor, *4(1)*:25
Adenine (NSC-14666), antitumor activity of, in animals, *1(2)*:383
Adenine nucleosides, structure-activity relationship, *1(1)*:1
Adenine phosphoribosyltransferase
inhibited by purine and pyrimidine analogs, *3(1)*:71
inhibitors of, *1(2)*:363
Adenocarcinoma 755 *see* Tumor systems in animals, Adenocarcinoma 755
Adenosine kinase
inhibited by purine and pyrimidine analogs, *3(1)*:71
inhibitors of, *2(1)*:237
Adriamycin (NSC-123127)
and its analogs as antitumor agents, *4(4)*:5
combined with radiation, effect on P815X2 cells in culture, *5(1)*:205
AKR lymphoma *see* Tumor systems in animals, lymphoma, AKR
Alkylating agents
chemotherapy of hamster tumors, *2(1)*:141
chemotherapy studies in an animal tumor spectrum, *1(2)*:403
effect of, on a spectrum of rat tumors, *3(1)*:231
evaluation of, in advanced L1210 leukemia in mice, *2(1)*:65
evaluation of, in advanced L1210 leukemia in mice, *3(1)*:1
methanesulfonates: relationship of structure to antitumor activity, *3(1)*:137
potential, quinones as anticancer agents, *4(4)*:23
***p*-Aminobenzoylglutamic acids**, relationship of structure to antitumor activity, *1(2)*:273
Antibiotics
chemotherapy of hamster tumors, *2(1)*:141
chemotherapy studies in an animal spectrum, *1(2)*:403
effect of, on a spectrum of rat tumors, *3(1)*:231
evaluation of, in advanced L1210 leukemia in mice, *2(1)*:65
evaluation of, in advanced L1210 leukemia in mice, *3(1)*:1
from the sea as antineoplastic agents, *4(3)*:97
Antimetabolites
chemotherapy of hamster tumors, *2(1)*:141
chemotherapy studies in an animal spectrum, *1(2)*:403
effect of, on a spectrum of rat tumors, *3(1)*:231
Arboviruses, cytolytic activity of, in murine leukemic lymphoblasts, *2(1)*:57

B

BCNU (NSC-409962), influence of the host on the effectiveness of, against advanced L1210 leukemia, *2(1)*:67
Benzothiazoles, chemotherapy studies on experimental mouse tumors, *2(1)*:177
1,3-Bis(2-chloroethyl)-1-nitrosourea *see* BCNU
Bleomycin (NSC-125066), combined with radiation, effect on CX-1B and HeLa cells in culture, *5(1)*:205
B16 melanoma *see* Tumor systems in animals, B16 melanoma
Breast cancer *see* Tumor systems in animals, adenocarcinoma of breast

C

CA 755 *see* Tumor systems in animals, Adenocarcinoma 755
Cancer, breast, solid tumor animal model therapeutically predictive for, *5(1)*:89
Cancer Chemotherapy National Service Center *see* CCNSC
Carcinogenesis, induced by purine-*N*-oxides, *1(1)*:383
Carcinoma 755 (Ca 755) *see* Tumor systems in animals, Adenocarcinoma 755
CCNSC protocols, used for screening Philippine medicinal plants for anticancer agents, *2(1)*:135
Cell cycles
biologic characterization of sc implanted Lewis lung tumor, *3(1)*:325
considerations of sc implanted B16 melanoma as a model for potential anticancer agents, *3(1)*:315
Cell kinetics
and tumor models, *5(1)*:83
biochemical aspects of drug combinations, *4(1)*:115
biochemical rationales for the selection of combinations of chemotherapeutic agents, *4(1)*:131
combination therapy: some concepts and results, *4(1)*:137
quinone natural products: streptonigrin and lapachol structure-activity relationships, *4(4)*:11
Cell lines
CX-1B, effect of simultaneous administration of bleomycin and radiation therapy, *5(1)*:205
HeLa, effect of simultaneous administration of bleomycin and radiation therapy, *5(1)*:205
KB cells
growth inhibition by 3837 compounds tested for antitumor activity: comparison with microbial assays, *2(1)*:27
in vitro, compared with L1210 cells in vivo and in vitro, *2(1)*:1

methanesulfonates: relationship of structure to antitumor activity, *3(1)*:137
quinone structure-antitumor activity relationships, *4(4)*:3
relationship of structure of purine and pyrimidine nucleosides to antitumor activity, *1(1)*:1
structure-antitumor activity relationships among quinone derivatives, *4(2)*:1
Taiwan plants for antitumor activity, *4(3)*:1
L5178Y, cytolytic activity of arboviruses in, *2(1)*:57
L1210 leukemia, cytotoxicity assays with, in vitro: comparison with L1210 in vivo and KB cells in vitro, *2(1)*:1
P815X2, effect of simultaneous administration of radiation and adriamycin, *5(1)*:205
relationship of structure to antitumor activity in compounds related to folic acid, *1(2)*:273
Cells, cultured
biochemical rationale for the selection of combinations of chemotherapeutic agents, *4(1)*:131
combination therapy: some concepts and results, *4(1)*:137
complement to in vivo approaches using combinations of chemotherapy and immunotherapy, *4(1)*:109
effect of daunorubicin and its derivatives on L1210 leukemia cells, *4(4)*:5
for the evaluation of irradiation and drug combinations, *5(1)*:205
inhibitors of purine metabolism in Ehrlich ascites tumor cells, *3(1)*:95
Central nervous system, theoretical techniques for understanding drugs acting on, *4(4)*:49
Clinical studies: combination of agents
interaction of experimental and clinical studies in combined modality treatment, *5(1)*:235
planning: interaction of experimental and clinical studies, *4(1)*:3
rationale of combined modality therapy for cancer, *4(1)*:13
Clinical studies: single agents
adriamycin and its analogs against various tumors, *4(4)*:5
lapachol in tumor treatment, *4(4)*:27
Cod liver oil, antineoplastic substances from, *4(3)*:97
Coenzyme Q_{10} (NSC-140865), and analogs in cancer treatment, *4(4)*:19
Combination therapy: animal studies
actinomycin D and γ-radiation against the Ridgway osteogenic sarcoma, *5(1)*:225
approaches to rat, mouse, and hamster tumors, *4(1)*:99
biochemical aspects of, *4(1)*:115
biochemical rationale for the selection of combinations, *4(1)*:131
cell survival systems for evaluation of irradiation and drug combinations, *5(1)*:205
collection and presentation of data, *4(1)*:167
concepts and results, *4(1)*:137
considerations for design and analysis, *4(1)*:157
detected in L1210 leukemia, *4(1)*:33
effect of nitrosourea-fluorinated pyrimidine combinations on mouse colon tumor models, *5(1)*:169
for spontaneous AKR lymphoma, *4(1)*:53
ICRF-159 plus *cis*-dichlorodiammineplatinum(II) or daunorubicin in L1210 leukemia, *4(1)*:45
immunologic and chemotherapeutic parameters in a model breast tumor system, *4(1)*:25
immunotherapy plus chemotherapy using in vivo and in vitro methods, *4(1)*:109
potentially active drug combinations detected in mouse tumor systems, *4(1)*:33
radiotherapy plus various agents for P388 lymphocytic leukemia in vivo, *4(1)*:73
statistical designs for, *4(1)*:151
Combination therapy: clinical studies *see* Clinical studies: combination of agents
Computers in combination chemotherapy: considerations for design and analysis, *4(1)*:157
Computers, management and analysis of mortality data obtained by treating small experimental animals with anticancer drugs, *5(1)*:243
Copper, antitumor activity of, *1(2)*:383
Cyclophosphamide (NSC-26271)
combination therapy in a model breast tumor system, *4(1)*:25
combined with radiotherapy in im implanted B16 melanoma, an animal model, *5(1)*:215
Cytosine nucleosides, structure-activity relationship, *1(1)*:1

D

Daunomycin *see* Daunorubicin
Daunorubicin (NSC–83142)
as an antitumor agent, *4(4)*:5
plus ICRF-159 against L1210 leukemia, *4(1)*:45
7-Deazapurine ribofuranosides *see* Pyrrolopyrimidine ribofuranosides
***cis*-Dichlorodiammineplatinum(II) (NSC–119875),** plus ICRF-159 against L1210 leukemia, *4(1)*:45
DNA synthesis, effect of daunorubicin and its derivatives on, *4(4)*:5
Drug design
comparison of Hansch and Free-Wilson methods for structure-activity correlation, *4(4)*:39
discussion of the extrathermodynamic approach, *4(4)*:37
extrathermodynamic approach to, *4(4)*:35
pattern recognition, *4(4)*:43
structure-activity relationships in, *4(4)*:51
structure-activity techniques in the treatment of antitumor drugs, *4(4)*:41
theoretical techniques for understanding drugs acting on the central nervous system, *4(4)*:49
use of quantum chemistry in development and analysis of anticancer drugs, *4(4)*:47
Drug screening
considerations of sc implanted B16 melanoma as a model for potential anticancer agents, *3(1)*:315
cornerstone of chemotherapy, *3(1)*:309
mouse ependymoblastoma as an experimental model for, *4(4)*:53
Drug synergism, therapeutic aspects, *4(1)*:147

E

Echinoderms, antineoplastic substances from, *4(3)*:97
Ehrlich ascites tumor *see* Tumor systems in animals, Ehrlich ascites
Ependymoblastoma *see* Tumor systems in animals, ependymoblastoma
Erythrocytes
human, inhibitors of hypoxanthine-guanine phosphoribosyltransferase in, *3(1)*:87
human, inhibitors of nucleoside and nucleotide metabolism in, *3(1)*:71
Escherichia coli, growth inhibition by 3837 compounds tested for antitumor activity: comparison of tumor cell culture and microbial assays, *2(1)*:27
Extrathermodynamic approach
discussion of, *4(4)*:37
to drug design, *4(4)*:35

F

5-Fluorouracil (NSC–19893), combined with radiotherapy in im implanted B16 melanoma, an animal model, *5(1)*:215
Folic acids
effect of, on a spectrum of rat tumors, *3(1)*:231
relationship of structure to antitumor activity in compounds related to, *1(2)*:273

G

Guanine nucleosides, structure-activity relationship, *1(1)*:1
Guanyl hydrazones, chemotherapy studies on experimental tumors, *2(1)*:177

H

Halopurine nucleosides, structure-activity relationship, *1(1)*:1
Hamster tumors, chemotherapy of, *2(1)*:141
Hydrazines, chemotherapy studies in an animal spectrum, *1(2)*:403
Hypoxanthine, inhibitors of metabolism in Ehrlich ascites tumor cells in vitro, *3(1)*:95
Hypoxanthine guanine phosphoribosyltransferase, inhibitors of, *3(1)*:87
Hypoxanthine nucleosides, structure-activity relationship, *1(1)*:1

I

ICRF–159 (NSC–129943)
combined with various other agents against L1210 leukemia, *4(1)*:33
enhancement of antitumor effectiveness of, against early L1210 leukemia by combination with *cis*-dichlorodiammineplatinum(II) or daunorubicin, *4(1)*:45
Imidazole carboxamides, evaluation of, in advanced L1210 leukemia in mice, *3(1)*:1
Imidazole furanosides, structure-activity relationship, *1(1)*:1
Immunology, and chemotherapeutic parameters in a model breast tumor system, *4(1)*:25
Immunotherapy
antineoplastic substances from the sea, *4(3)*:97
plus chemotherapy using in vivo and in vitro methods, *4(1)*:109
Isoquinolines, chemotherapy studies on experimental mouse tumors, *2(1)*:199

K

KB cells *see* Cell lines, KB

L

L5178Y lymphoma *see* Tumor systems in animals, lymphoma, L5178Y
Lactobacillus casei, growth inhibition by 3837 compounds tested for antitumor activity: comparison of tumor cell culture and microbial assays, *2(1)*:27
Lapachol (NSC–11905)
and streptonigrin, quinone natural products, structure-activity relationships, *4(4)*:11
early clinical studies with, *4(4)*:27
Lewis lung carcinoma *see* Tumor systems in animals, carcinoma, Lewis lung
Lymphoblasts, cytolytic activity of arboviruses in murine leukemia, *2(1)*:59
Lymphocytes
human, activity of succinate dehydrogenase coenzyme Q_{10} reductase in, *4(4)*:19
use of, to complement in vivo approaches using combinations of chemotherapy and immunotherapy, *4(1)*:109

M

Magnesium, from the sea as an antineoplastic agent, *4(3)*:97
6-Mercaptopurine (NSC–755; 6–MP), antitumor activity of, *1(2)*:383
Mercaptopurine nucleosides, structure-activity relationship, *1(1)*:1
Methanesulfonates, relationship of structure to antitumor activity, *3(1)*:137
Methotrexate (NSC–740), influence of the host on the effectiveness of, against advanced L1210 leukemia, *2(1)*:67
Mice, influence of the host strain on the effectiveness of methotrexate and BCNU, *2(1)*:67

Mitomycin C (NSC–26980)
combination chemotherapy in a model breast tumor system, *4(1)*:25
derivatives, structure-activity relationships in the treatment of L1210 leukemia, *3(1)*:121
influence of schedule of administration in the treatment of L1210 leukemia, *3(1)*:111
Model systems
biologic characteristics of tumor progression in the mouse mammary gland, *5(1)*:127
combination chemotherapy: considerations for design and analysis, *4(1)*:157
combination therapy: some concepts and results, *4(1)*:137
considerations of sc implanted B16 melanoma for potential anticancer agents, *3(1)*:315
im implanted B16 melanoma as an animal model for combined radiotherapy and chemotherapy studies, *5(1)*:215
immunologic and chemotherapeutic parameters in a breast tumor system, *4(1)*:25
in vitro methods to complement in vivo approaches using combinations of chemotherapy and immunotherapy, *4(1)*:109
kinetics and tumor models, *5(1)*:83
mouse colon tumor models for experimental therapy, *5(1)*:169
mouse ependymoblastoma for screening potential antineoplastic drugs, *4(4)*:53
new models for cancer chemotherapy, *5(1)*:133
potential for murine tumor models in surgical adjuvant chemotherapy, *5(1)*:187
potentially useful combination chemotherapy detected in L1210 leukemia, *4(1)*:33
preliminary drug trials in a renal cell carcinoma animal model, *5(1)*:145
Ridgway osteogenic sarcoma—a promising laboratory model for special therapeutic trials against an advanced-staged, drug-sensitive animal tumor system, *5(1)*:151
solid tumor animal model therapeutically predictive for human breast cancer, *5(1)*:89
statistical designs for combination therapy, *4(1)*:151

N

National Cancer Institute Drug Research and Development program, *4(4)*:33
Nitrosourea compounds
combined with fluorinated pyrimidines in mouse colon tumor models, *5(1)*:169
evaluation of, in advanced L1210 leukemia in mice, *3(1)*:1
NSC–740 *see* Methotrexate
NSC–752 *see* 6-Thioguanine
NSC–755 *see* 6-Mercaptopurine
NSC–3053 *see* Actinomycin D
NSC–11905 *see* Lapachol
NSC–14664 *see* Xanthine
NSC–14666 *see* Adenine
NSC–26271 *see* Cyclophosphamide
NSC–26980 *see* Mitomycin C
NSC–45383 *see* Streptonigrin
NSC–83142 *see* Daunorubicin
NSC–119875 *see cis*-Dichlorodiammineplatinum(II)
NSC–123127 *see* Adriamycin
NSC–129943 *see* ICRF-159
NSC–140865 *see* Coenzyme Q_{10}
NSC–409962 *see* BCNU

P

P388 leukemia *see* Tumor systems in animals, P388 leukemia
Pattern recognition *see* Structure-activity relationships
Philippine medicinal plants, as anticancer agents, *2(1)*:135
Phthalanilides
chemotherapy studies in an animal spectrum, *1(2)*:403
evaluation of, in advanced L1210 leukemia in mice, *2(1)*:65
Physical chemistry, and other theoretical techniques for understanding drugs acting on the central nervous system, *4(4)*:49
Piperazine dimethanesulfonates, relation of structure to antitumor activity, *3(1)*:137
Plant extracts
assays with L1210 in vivo and in vitro and KB cells in vitro, *2(1)*:1
screening of Philippine medicinal, for anticancer agents using CCNSC protocols, *2(1)*:135
screening of Taiwan plants for antitumor activity, *4(3)*:1
Porifera, antineoplastic substances from, *4(3)*:97
Protocols for drug screening and clinical studies
collection and presentation of combination data, *4(1)*:167
planning combined therapy: interaction of experimental and clinical studies, *4(1)*:3
using Philippine medicinal plants, *2(1)*:135
Pteridines, relationship of structure to antitumor activity, *1(2)*:273
Pteroic acids, relationship of structure to antitumor activity, *1(2)*:273
Pteroyl glutamic acids, relationship of structure to antitumor activity, *1(2)*:273
Purine analogs and derivatives (*see also* specific compounds)
chemotherapy of hamster tumors, *2(1)*:141
chemotherapy studies in an animal spectrum, *1(2)*:403
effect of, on a spectrum of rat tumors, *3(1)*:231
evaluation of, in advanced L1210 leukemia in mice, *3(1)*:1
inhibitors of adenine phosphoribosyltransferase, *1(2)*:363
inhibitors of adenosine kinase, *2(1)*:237
inhibitors of hypoxanthine-guanine phosphoribosyltransferase, *3(1)*:87
inhibitors of nucleoside and nucleotide metabolism, *3(1)*:71
inhibitors of purine biosynthesis de novo, *1(2)*:375

inhibitors of purine metabolism in Ehrlich ascites tumor cells in vitro, *3(1)*:95
Purine nucleosides (*see also* specific compounds)
inhibition of transport in human erythrocytes, *3(1)*:71
inhibitors of adenine phosphoribosyltransferase, *1(2)*:363
inhibitors of adenosine kinase, *2(1)*:237
inhibitors of purine biosynthesis de novo, *1(2)*:375
methanesulfonates: relationship of structure to antitumor activity, *3(1)*:137
structure-activity relationship, *1(1)*:1
Purine-*N*-oxides, antitumor activity of, and effect of selected compounds on tumors induced by, *1(2)*:383
Purines (*see also* specific compounds)
biosynthesis of, in presence of purine nucleoside inhibitors, *1(2)*:375
evaluation of, in advanced L1210 leukemia in mice, *2(1)*:67
inhibitors of adenine phosphoribosyltransferase, *1(2)*:363
inhibitors of adenosine kinase, *2(1)*:237
inhibitors of de novo synthesis, *3(1)*:71
pattern recognition in antitumor activity, *4(4)*:45
Pyrimidine analogs and derivatives (*see also* specific compounds)
chemotherapy of hamster tumors, *2(1)*:141
chemotherapy studies in an animal tumor spectrum, *1(2)*:403
chemotherapy studies on experimental mouse tumors, *2(1)*:199
effect of, on a spectrum of rat tumors, *3(1)*:231
evaluation of, in advanced L1210 leukemia in mice, *3(1)*:1
inhibitors of hypoxanthine-guanine phosphoribosyltransferase, *3(1)*:87
inhibitors of nucleoside and nucleotide metabolism, *3(1)*:71
Pyrimidine nucleosides (*see also* specific compounds)
inhibitors of adenine phosphoribosyltransferase, *1(2)*:363
inhibitors of adenosine kinase, *2(1)*:237
methanesulfonates: relationship of structure to antitumor activity, *3(1)*:137
structure-activity relationship, *1(1)*:1
Pyrimidines (*see also* specific compounds)
and pteroyl glutamic and pteroic acid derivatives, relationship of structure to antitumor activity, *1(2)*:273
combined with nitrosoureas in mouse colon tumor models, *5(1)*:169
evaluation of, in advanced L1210 leukemia in mice, *2(1)*:67
inhibitors of adenine phosphoribosyltransferase, *1(2)*:363
inhibitors of adenosine kinase, *2(1)*:237
pattern recognition in antitumor activity, *4(4)*:45
Pyrrolopyrimidine ribofuranosides, structure-activity, *1(1)*:1

Q

Quantum chemistry
and other theoretical techniques for understanding drugs acting on the central nervous system, *4(4)*:49
in development and analysis of anticancer drugs, *4(4)*:47
in drug design, *4(4)*:51
Quinolines
chemotherapy of hamster tumors, *2(1)*:141
effect of, on a spectrum of rat tumors, *3(1)*:231
Quinones
as anticancer agents: potential bioreductive alkylating agents, *4(4)*:23
natural products: streptonigrin and lapachol structure-activity relationships, *4(4)*:11
structure-antitumor activity relationships, *4(2)*:1; *4(4)*:3

R

Radiation therapy
and actinomycin D against the Ridgway osteogenic sarcoma, *5(1)*:225
and drug combinations, cell survival systems for the evaluation of, *5(1)*:205
and 5-fluorouracil or cyclophosphamide in im implanted B16 melanoma, an animal tumor model, *5(1)*:215
plus various agents for P388 lymphocytic leukemia in vivo, *4(1)*:73

S

S180 Crocker (S180) *see* Tumor systems in animals, Sarcoma 180, Crocker
Screening
biologic characterization of the sc implanted Lewis lung tumor, *3(1)*:325
consideration of the sc implanted B16 melanoma as a screening model for potential anticancer agents, *3(1)*:315
cornerstone of chemotherapy, *3(1)*:309
impact upon screeners of the front-end redesign, *5(1)*:253
modified protocol for the testing of new synthetics in the L1210 lymphoid leukemia murine model, *5(1)*:15
preclinical characterization of candidate antitumor drugs, *5(1)*:21
statistical properties of the L1210 mouse leukemia tumor system in primary, *5(1)*:5
Seawater, antineoplastic substances from, *4(3)*:97
Semicarbazones
chemotherapy studies in an animal spectrum, *1(2)*:403
evaluation of, in advanced L1210 leukemia in mice, *2(1)*:67
Statistical designs, for experiments in combination therapy, *4(1)*:151
Statistics
combination chemotherapy: considerations for design and analysis, *4(1)*:157
statistical properties of the L1210 mouse leukemia tumor system in primary screening, *5(1)*:5
Steroids
chemotherapy of hamster tumors, *2(1)*:141
chemotherapy studies in an animal spectrum, *1(2)*:403
effect of, on a spectrum of rat tumors, *3(1)*:231

methanesulfonates: relationship of structure to antitumor activity, *3(1)*:137
Streptonigrin (NSC–45383), and lapachol, quinone natural products, structure-activity relationships, *4(4)*:11
Structure-activity relationships
adriamycin and its analogs as antitumor agents, *4(4)*:5
antitumor activity among quinone derivatives, *4(2)*:1
comparison of Hansch and Free-Wilson methods, *4(4)*:39
discussion of extrathermodynamic approach, *4(4)*:37
discussion of pattern recognition, *4(4)*:45
extrathermodynamic approach to drug design, *4(4)*:35
folic acid-related compounds and antitumor activity, *1(2)*:273
general comments, *4(4)*:51
methanesulfonates: relationship to antitumor activity, *3(1)*:137
mitomycin C and derivatives in the treatment of L1210 leukemia, *3(1)*:121
pattern recognition, *4(4)*:43
purines and purine-*N*-oxides with antitumor activity, *1(2)*:383
purine and pyrimidine nucleosides with antitumor activity, *1(1)*:1
quinone natural products: streptonigrin and lapachol, *4(4)*:11
quinones as antitumor agents, *4(4)*:3
treatment of antitumor drugs, *4(4)*:41
Sugar phosphates, inhibitors of adenine phosphoribosyltransferase, *1(2)*:363
Surgery plus chemotherapy
potential for murine tumor models in surgical adjuvant chemotherapy, *5(1)*:187
some concepts and results, *4(1)*:137

T

Taiwan plant extracts, screened as anticancer agents, *4(3)*:1
Taper liver tumor *see* Tumor systems in animals, Taper liver tumor
Terephthanilides, chemotherapy studies in an animal spectrum, *1(2)*:403
Tetrahymena pyriformis, growth inhibition by 3837 compounds tested for antitumor activity: comparison of tumor cell culture and microbial assays, *2(1)*:27
6-Thioguanine (NSC–752), in combination therapy in a model breast tumor system, *4(1)*:25
Thioguanine nucleosides, structure-activity relationship, *1(1)*:1
Thiosemicarbazones
chemotherapy studies on experimental mouse tumors, *2(1)*:177,199
Thioxanthones, chemotherapy studies on experimental mouse tumors, *2(1)*:177
Tumor systems in animals
adenocarcinoma
755
chemotherapy studies on, *2(1)*:177,199
methanesulfonates: relationship of structure to antitumor activity, *3(1)*:137
pattern recognition in treatment, *4(4)*:45
quinone structure-antitumor activity relationships, *4(4)*:3
quinones as anticancer agents: potential bioreductive alkylating agents, *4(4)*:23
relationship of structure of purine and pyrimidine nucleosides to antitumor activity, *1(1)*:1
relationship of structure to antitumor activity in compounds related to folic acid, *1(2)*:273
screening of Philippine medicinal plants using CCNSC protocols, *2(1)*:135
structure-antitumor activity relationship among quinone derivatives, *4(2)*:1
DMBA-induced, approaches to chemotherapy in, *4(1)*:99
E0771, chemotherapy studies in, *1(2)*:403
mammary, immunologic and chemotherapeutic parameters, *4(1)*:25
pancreas No. 1, in Fortner hamsters, chemotherapy of, *2(1)*:141
small bowel No. 1, in Fortner hamsters, chemotherapy of, *2(1)*:141
carcinoma
1025 (*see also* Tumor systems in animals, Adenocarcinoma 755), chemotherapy studies in animals, *1(2)*:403
C3H mammary
approaches to chemotherapy in, *4(1)*:99
potential for, in surgical adjuvant chemotherapy, *5(1)*:187
colon 26, potential for, in surgical adjuvant chemotherapy, *5(1)*:187
Ehrlich ascites
antineoplastic substances from the sea, *4(3)*:97
chemotherapy studies on, *1(2)*:403, *2(1)*:177, 199
inhibitors of adenosine kinase from, *2(1)*:237
inhibitors of adenine phosphoribosyltransferase from, *2(1)*:363
inhibitors of nucleoside and nucleotide metabolism, *3(1)*:71
inhibitors of purine metabolism of, in vitro, *3(1)*:95
Lewis lung
chemotherapy studies on, *2(1)*:177,199
iv implanted, growth characteristics and chemotherapeutic response of, *5(1)*:111
kinetic parameters for, *5(1)*:83
methanesulfonates: relationship of structure to antitumor activity, *3(1)*:137
potential for, in surgical adjuvant chemotherapy, *5(1)*:187
relationship of structure of purine and pyrimidine nucleosides to antitumor activity, *1(1)*:1
relationship of structure to antitumor activity in compounds related to folic acid, *1(2)*:273
sc implanted, biologic characterization of, *3(1)*:325
renal cell, preliminary drug trials in BALB/c mice with, *5(1)*:145
colon tumors, models for experimental therapy, *5(1)*:169
ependymoblastoma, mouse, for screening potential antineoplastic drugs, *4(4)*:53

fibrosarcoma, induced by purine-*N*-oxides, effect of selected compounds on, *1(2)*:383
induced by purine-*N*-oxides, antitumor activity of purine-*N*-oxides and effect of selected compounds on, *1(2)*:383
leukemia
C1498 myelogenous, chemotherapy studies on, *2(1)*:177, 199
L1210
adriamycin and its analogs in the treatment of, *4(4)*:5
advanced, evaluation of antileukemic agents in, *2(1)*:65
advanced, evaluation of antileukemic agents in mice with, *3(1)*:1
antineoplastic substances from the sea, *4(3)*:97
biochemical rationale for the selection of combinations of chemotherapeutic agents, *4(1)*:131
chemotherapy studies on, *2(1)*:177,199
coenzyme Q_{10} in the treatment of, *4(4)*:19
combination therapy: some concepts and results, *4(1)*:137
cytotoxicity assays in vitro: comparison with L1210 in vivo and KB cells in vitro, *2(1)*:1
enhancement of effectiveness of ICRF-159 with *cis*-dichlorodiammineplatinum(II) or daunorubicin, *4(1)*:45
influence of schedule of administration of mitomycin C in the treatment of, *3(1)*:111
lymphoid leukemia murine model, modified protocol for the testing of new synthetics in, *5(1)*:15
methanesulfonates: relationship of structure to antitumor activity, *3(1)*:137
pattern recognition in the treatment of, *4(4)*:45
potentially useful combinations of chemotherapy detected in, *4(1)*:33
purine nucleoside inhibitors of purine synthesis de novo in, *1(2)*:373
quinone structure-antitumor activity relationships, *4(4)*:3
relationship of structure of purine and pyrimidine nucleosides to antitumor activity, *1(1)*:1
relationship of structure to antitumor activity in compounds related to folic acid, *1(2)*:273
screening of Philippine medicinal plants using CCNSC protocols, *2(1)*:135
statistical properties of, in primary screening, *5(1)*:5
structure-antitumor activity relationships among quinone derivatives, *4(2)*:1
structure-activity relationships for mitomycin C derivatives in the treatment of, *3(1)*:121
Taiwan plants for antitumor activity, *4(3)*:1
P388
combined radiotherapy and chemotherapy in vivo, *4(1)*:73
screening of Philippine medicinal plants using CCNSC protocols, *2(1)*:135
Taiwan plants for antitumor activity, *4(3)*:1
lymphoma
AKR spontaneous, combination chemotherapy for, *4(1)*:53
L5178Y, chemotherapy studies in, *2(1)*:177,199
lymphosarcoma, Mecca, chemotherapy studies in, *1(2)*:403
mammary, $CD8F_1$, therapeutically predictive for human breast cancer, *5(1)*:89
mammary tumor virus, biologic characteristics of tumor progression in, *5(1)*:127
melanoma
B16
approaches to chemotherapy in, *4(1)*:99
chemotherapy studies in, *1(2)*:403, *2(1)*:177,199
considerations of, implanted sc as a screening model for potential anticancer agents, *3(1)*:315
im implanted, as an animal model for combined γ-radiation therapy and chemotherapy studies, *5(1)*:215
kinetic parameters for, *5(1)*:83
potential for, in surgical adjuvant chemotherapy, *5(1)*:187
melanotic No. 1, approaches to chemotherapy in, *4(1)*:99
plasmacytoma
approaches to chemotherapy in, *4(1)*:99
in the hamster, potential for, in surgical adjuvant chemotherapy, *5(1)*:187
sarcoma
134, in Crabb hamsters, chemotherapy of, *2(1)*:141
180, Crocker
chemotherapy studies in, *2(1)*:177,199
coenzyme Q_{10} in the treatment of, *4(4)*:19
methanesulfonates: relationship of structure to antitumor activity, *3(1)*:137
quinone structure-antitumor activity relationships, *4(4)*:3
quinones as anticancer agents: potential bioreductive alkylating agents, *4(4)*:23
relationship of structure of purine and pyrimidine nucleosides to antitumor activity, *1(1)*:1
relationship of structure to antitumor activity in compounds related to folic acid, *1(2)*:273
screening of Philippine medicinal plants using CCNSC protocols, *2(1)*:135
structure-antitumor activity relationships among quinone derivatives, *4(2)*:1
osteogenic No. 1, approaches to chemotherapy in, *4(1)*:99
Ridgway osteogenic
actinomycin D and γ-radiation therapy against, *5(1)*:225
chemotherapy studies in, *1(2)*:403
kinetic parameters for, *5(1)*:83
a promising laboratory model for special therapeutic trials against an advanced-staged, drug-sensitive animal tumor system, *5(1)*:151
T241, chemotherapy studies in animals, *1(2)*:403
rats, effect of compounds on a spectrum of, *3(1)*:231
Taper liver tumor, chemotherapy studies in animals, *1(2)*:403
Walker 256 carcinosarcoma
chemotherapy studies in animals, *1(2)*:403

methanesulfonates: relationship of structure to antitumor activity, *3(1)*:137
quinone structure-antitumor activity relationships, *4(4)*:3
relationship of structure of purine and pyrimidine nucleosides to antitumor activity, *1(1)*:1
relationship of structure to antitumor activity in compounds related to folic acid, *1(2)*:273
screening of Philippine medicinal plants using CCNSC protocols, *2(1)*:135
structure-antitumor activity relationships among quinone derivatives, *4(2)*:1
Taiwan plants for antitumor activity, *4(3)*:1

U

Uracil nucleosides, structure-activity relationship, *1(1)*:1
Urea compounds, evaluation of, in advanced L1210 leukemia in mice, *2(1)*:67, *3(1)*:1

W

Walker 256 carcinosarcoma *see* Tumor systems in animals, Walker 256 carcinosarcoma

X

Xanthine (NSC–14664), antitumor activity of, *1(2)*:383
Xanthine nucleosides, structure-activity relationship, *1(1)*:1
Xenografts
development of, from human tumors, new models for cancer chemotherapy, *5(1)*:133
development of transplantable xenografts from human tumors, *5(1)*:133

Subject Index

A

Adenocarcinoma 755 *see* Tumor systems in animals, Adenocarcinoma 755
Adenocarcinoma, bronchogenic, large-cell and small-cell, polychemotherapy with adriamycin, *6(2)*:353
Adriamycin (NSC–123127)
activity in genitourinary and gynecologic malignancies, *6(2)*:297
alone and in combination for soft tissue and bony sarcomas, *6(2)*:271
alone or in combination with other agents in the treatment of lymphomas, *6(2)*:375
arterial infusion studies, *6(2)*:187
cardiomyopathy
an overview with determination of risk factors, *6(2)*:195
clinical studies, *6(2)*:203
clinicopathologic correlation, *6(2)*:215
in children, *6(2)*:209
pathologic effects of, in experimental systems, *6(2)*:159
cell interactions: determinants of selective toxicity of, and daunorubicin, *6(2)*:107
clinical pharmacology of, *6(2)*:183
combination usage of, in malignant lymphomas, *6(2)*:381
compared with daunorubicin against L1210 leukemia, *3(1)*:33
current status of studies, *4(3)*:47
daunorubicin and some structural analogs: macromolecular interactions and their biologic consequences, *6(2)*:115
development of, *6(2)*:83
DNA complex: preliminary results in mice and man, *6(2)*:131
experimental tumor activity of, *6(2)*:137
mode and mechanism of action, *6(2)*:91
new chemical developments and analogs, *6(2)*:123
pharmacology in rabbits, *6(2)*:153
phase II study in childhood solid tumors, *6(2)*:267
plus methotrexate in patients with disseminated breast cancer, *6(2)*:335
plus other agents in squamous cell lung cancer, *6(2)*:361
plus vincristine and methotrexate in patients with disseminated breast cancer, *6(2)*:339
plus vincristine, cyclophosphamide, and melphalan in the primary treatment of osteogenic sarcoma, *6(2)*:315
polychemotherapy with, in bronchogenic carcinoma, *6(2)*:353
rational bases for combination therapy, *6(2)*:227
response of bronchogenic carcinoma, *6(2)*:349
studies at the Istituto Nazionale Tumori, Milan, *6(2)*:231
studies in adult patients, *6(2)*:253
studies of treatment in the United States, *6(2)*:247
survival and cell kinetic effects of, on CHO cells, *6(2)*:147
toxicity studies in animals, *6(2)*:177
toxicology, a practical approach, *6(2)*:191
therapy for thyroid carcinoma, *6(2)*:283
treatment in advanced breast cancer, *6(2)*:329
treatment in breast cancer: overview of studies, *6(2)*:319
treatment in hematologic disorders, *6(2)*:369
treatment in lung cancer, European studies, *6(2)*:343
treatment in pediatric malignancies, *6(2)*:259
treatment of 87 patients with osteosarcoma, *6(2)*:305
treatment of various tumors—thoughts for the future, *6(2)*:389
Animals and animal care, *3(2)*:37
2,2′-(9,10-Anthrylenedimethylene)bis[2-thiopseudourea], dihydrochloride, dihydrate (NSC–56054), clinical brochure, *1(1)*:153
L-Asparaginase (NSC–109229), improvement in the therapeutic index of methotrexate by, *6(1)*:37
Austrian Study Group, chemotherapeutic studies in bronchogenic carcinoma, *4(2)*:207
5-Azacytidine (NSC–102816)
in preclinical and clinical trials, *4(2)*:265
pharmacology report, *3(1)*:69
Azotomycin (NSC–56654), clinical brochure, *1(1)*:207

B

BCNU (NSC–409962)
alone or combined with other agents in advanced gastrointestinal cancer, *4(3)*:27
clinical brochure, *1(1)*:115
formulation for iv use, *4(3)*:7
phase II study in disseminated breast cancer, *3(1)*:29
toxicology and pharmacology, *4(3)*:13
treatment of brain tumors, *4(3)*:21
treatment of Hodgkin's disease, *3(1)*:33
treatment of several tumors, *4(3)*:35
BIC (NSC–82196)
clinical brochure, *1(1)*:63
treatment of various tumors, *3(1)*:33
Bleomycin (NSC–125066)
marked with radioactive isotopes in cancer treatment, *4(2)*:245
plus other agents in squamous cell lung cancer, *6(2)*:361
preclinical toxicologic evaluation in rhesus monkeys, *4(1)*:31
Blood platelets, transfusion procedures, *1(1)*:1
Blood transfusion, routine, obstacles to support of myelosuppressive patients, *4(3)*:151

B16 melanoma *see* Tumor systems in animals, B16 melanoma
Brain cancer *see* Carcinoma in man, brain
Breast carcinoma *see* Carcinoma in man, breast
Bronchogenic carcinoma *see* Carcinoma in man, lung
Burkitt's lymphoma, membrane transport of methotrexate in, *6(1)*:73

C

Camptothecin (NSC–100880), toxicity studies in dogs, monkeys, rats, and mice, *5(1)*:25
Carcinoma in man
brain
irradiation plus chemotherapy in the initial treatment of small cell carcinoma, *4(2)*:39
treatment with nitrosoureas, *4(3)*:21
breast
adriamycin treatment, *6(2)*:389
adriamycin treatment: overview of studies, *6(2)*:319
advanced, adriamycin treatment in, *6(2)*:329
disseminated, combination therapy with adriamycin and methotrexate, *6(2)*:335
disseminated, phase II study, *3(1)*:29
disseminated, treatment with adriamycin plus vincristine and methotrexate, *6(2)*:339
metastatic, adriamycin in the treatment of, in the United States, *6(2)*:247
genitourinary, adriamycin activity in, *6(2)*:297
gastrointestinal, advanced, therapy with the nitrosoureas, *4(3)*:27
gynecologic, adriamycin activity in, *6(2)*:297
liver, childhood, adriamycin phase II study, *6(2)*:267
lung
adenocarcinoma, bronchogenic, large-cell and small-cell, polychemotherapy with adriamycin, *6(2)*:353
adjuvant chemotherapy trials, *4(2)*:119
adjuvant immunotherapy after incomplete resection, *4(2)*:293
adjuvant long-term chemotherapy with cyclophosphamide after radical resection, *4(2)*:125
adriamycin treatment, *6(2)*:389
adriamycin treatment, European studies, *6(2)*:343
biostatistics and data retrieval, *4(2)*:31
cell-mediated immunity: data, problems, and propositions, *4(2)*:279
chemotherapeutic studies by the Austrian Study Group, *4(2)*:207
chemotherapy in, *4(2)*:25
chemotherapy, National Cancer Institute of Milan, *4(2)*:231
chemotherapy, USSR, *4(2)*:251
comparative results of right pneumonectomy and sleeve lobectomy, *4(2)*:97
correlation of histologic types with cell kinetic studies, *4(2)*:69
diagnosis
observer variability and reliability, *4(2)*:55
staging and criteria of response to therapy, *4(2)*:17,303
epidemiology of different histologic types, *4(2)*:59
first international workshop for therapy, *4(2)*:5
frequency of residual and metastatic, in patients undergoing curative surgical resection, *4(2)*:63
immunologic treatment, *4(2)*:271
immunology and immunotherapy, *4(2)*:29
immunotherapy, nonspecific, preliminary results, *4(2)*:283
initial therapeutic trial of new drugs, *4(2)*:215
inoperable, phase II study of methyl-CCNU, *4(2)*:257
monochemotherapy with special reference to cell type, *4(2)*:177
morphologic classification, *4(2)*:299
new drugs available for study, *4(2)*:265
oat cell
remission rates, survival, and prognostic factors in combination chemotherapy, *4(2)*:199
treatment with cyclophosphamide and radiation therapy, *4(2)*:159
pathology of, *4(2)*:15
primary, photofluorographically detected, survival factors, *4(2)*:95
radiation therapy for, *4(2)*:145,153,311
radiation therapy techniques suitable for intercenter cooperative studies, *4(2)*:137
reliability of cytologic diagnosis, *4(2)*:79
remission rates, survival, and prognostic factors in combination chemotherapy, *4(2)*:199
response to adriamycin, *6(2)*:349
small cell
adenocarcinoma, polychemotherapy with adriamycin, *6(2)*:353
brain irradiation plus chemotherapy in initial treatment, *4(2)*:239
should initial treatment include systemic chemotherapy and brain irradiation?, *4(2)*:239
treatment with chemotherapy and radiotherapy, *4(2)*:171
squamous cell
animal model system, histogenesis, *4(2)*:43
combination chemotherapy, *6(2)*:361
malignancy-associated changes in oral and bronchial epithelial cells in sputum specimens, *4(2)*:73
remission rates, survival, and prognostic factors in combination chemotherapy, *4(2)*:199
treatment with methotrexate and radiation therapy, *4(2)*:157
surgeon's viewpoint on collaborative research, *4(2)*:307
surgery adjuvant studies, *4(2)*:109
surgery: prospects and priorities for clinical research, *4(2)*:19
treatment with or without RSV after pulmonary resection, *4(2)*:261
treatment with CCNU alone or in combination with other agents, *4(3)*:35
treatment with ICRF–159 plus radiation therapy, *4(2)*:243
treatment with new agents and combinations, *4(2)*:227
treatment with radiotherapy alone or in combination with atmospheric oxygen and 5-fluorouracil, *4(2)*:165

treatment with surgery and radiotherapy, National Cancer Institute of Milan, *4(2)*:101
treatment with surgery plus radiotherapy and surgery plus chemotherapy, *4(2)*:133
unresectable, cyclophosphamide as adjuvant to radiotherapy, *4(2)*:161
Veterans' Administration program, *4(2)*:7
ovary, adriamycin in pediatric malignancies, *6(2)*:259
thyroid gland, adriamycin therapy in, *6(2)*:283
Cats, mitomycin C toxicity in, *1(1)*:99
CCNU (NSC–79037)
alone or combined with other agents against bronchogenic carcinoma and Hodgkin's disease, *4(3)*:35
alone or combined with other agents in advanced gastrointestinal cancer, *4(3)*:27
clinical brochure, *1(1)*:115
formulation for iv use, *4(3)*:7
plus other agents in squamous cell lung cancer, *6(2)*:361
preclinical toxicologic evaluation of single iv infusion in dogs and monkeys, *5(1)*:53
toxicology and pharmacology, *4(3)*:13
treatment of brain tumors, *4(3)*:21
treatment of various tumors, *3(1)*:33
Cell division, cell kinetics and the chemotherapy of cancer, *2(1)*:23
Cell kinetics
adriamycin: mode and mechanism of action, *6(2)*:91
adriamycin, rational bases for combination therapy, *6(2)*:227
analysis of the cytotoxic determinants for methotrexate: a role for "free" intracellular drug, *6(1)*:51
and the chemotherapy of cancer, *2(1)*:23
determinants of selective toxicity of adriamycin and daunorubicin, *6(2)*:107
development of adriamycin, *6(2)*:83
effects of adriamycin, *6(2)*:147
guanazole effect on L1210 leukemia, *3(1)*:33
in lung cancer, correlation with histologic types, *4(2)*:69
in vitro phase-specificity screening, *3(1)*:7
membrane transport of methotrexate and other folate compounds: relevance to rescue protocols, *6(1)*:63
pharmacokinetics, *3(1)*:21
reports on ellipticine, 5-azacytidine, and cytosine arabinoside, *3(1)*:69
relevance to drug screening, *4(3)*:79
role of chemical structure in biochemical activity of daunorubicin, adriamycin, and some structural analogs: macromolecular interactions and their biologic consequences, *6(2)*:115
Cell line
CHO, survival and cell kinetic effects of adriamycin, *6(2)*:147
in vitro phase-specificity screening, *3(1)*:7
KB
in vivo-in vitro screening, *3(1)*:57
porfiromycin activity in, *1(1)*:81
protocol for drug screening, *3(2)*:17
lymphoma P288, determinants of selective toxicity of adriamycin and daunorubicin, *6(2)*:107
technical procedures for use in drug screening, *3(2)*:59
Cells, cultured
adriamycin: mode and mechanism of action, *6(2)*:91
membrane transport of methotrexate in human neoplastic tissue, *6(1)*:73
CF *see* Citrovorum factor
1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea *see* CCNU
1,3-bis-(2-Chloroethyl)-1-nitrosourea *see* BCNU
CHO cells *see* Cell line, CHO (Chinese hamster ovary)
Chromomycin A_3 (NSC–58514), in preclinical and clinical trials, *4(2)*:265
Citrovorum factor (NSC–3590)
plus methotrexate, high-dose, clinical trial of, toxicologic and therapeutic observations, *6(1)*:43
plus methotrexate, high-dose, toxicity in osteogenic sarcoma, *6(1)*:31
rescue for high-dose methotrexate: background and rationale, *6(1)*:3
rescue for high-dose methotrexate in children with osteosarcoma and other malignant tumors, *6(1)*:13
rescue of high-dose methotrexate, overview of protocols on clinical studies, *6(1)*:7
Clinical studies
interdisciplinary group on, biostatistics, *4(2)*:317
supportive care, *2(1)*:99
Clinical studies: combination of agents
adriamycin
plus methotrexate in patients with disseminated breast cancer, *6(2)*:335
plus other agents, rational bases for, *6(2)*:227
plus other agents in pediatric malignancies, *6(2)*:259
plus other agents in soft tissue and bony sarcomas, *6(2)*:271
plus other agents in the treatment of lymphomas, *6(2)*:375
plus other agents in the treatment of malignant lymphomas, *6(2)*:381
plus other agents in the treatment of various tumors, *6(2)*:253
plus various agents in the treatment of bronchogenic carcinoma, *6(2)*:353
plus vincristine and methotrexate in patients with disseminated breast cancer, *6(2)*:339
plus vincristine, cyclophosphamide, and melphalan in primary treatment of osteogenic sarcoma, *6(2)*:315
treatment of breast cancer: overview of studies, *6(2)*:319
treatment of hematologic disorders, *6(2)*:369
treatment of various tumors, *6(2)*:389
BCNU plus other agents in the treatment of Hodgkin's disease, *3(1)*:33
chemotherapy plus brain irradiation in the initial treatment of small cell carcinoma, *4(2)*:239
cyclophosphamide
after radical resection in bronchogenic carcinoma, *4(2)*:125
plus radiation therapy for oat cell carcinoma of the lung, *4(2)*:159
plus radiation therapy for unresectable bronchogenic carcinoma, *4(2)*:161
cytosine arabinoside plus other agents in the treatment of various tumors, *1(1)*:179
ICRF-159 plus radiotherapy in bronchogenic carcinoma, *4(2)*:243

immunotherapy
plus incomplete resection for bronchogenic carcinoma, *4(2)*:293
treatment of lung cancer, *4(2)*:271
leukemia, chronic granulocytic, guidelines for, *4(1)*:167
leukemia, chronic lymphocytic, guidelines for, *4(1)*:159
methods of study, *2(1)*:81
methotrexate
high-dose plus citrovorum factor in osteogenic sarcoma, *6(1)*:31
high-dose, plus citrovorum factor rescue, *6(1)*:7
high-dose plus citrovorum factor rescue for children with osteosarcoma and other malignant tumors, *6(1)*:13
high-dose plus citrovorum factor, toxicologic and therapeutic observations, *6(1)*:43
plus adriamycin and vincristine in patients with disseminated breast cancer, *6(2)*:339
plus adriamycin in patients with disseminated breast cancer, *6(2)*:335
plus citrovorum factor rescue, *6(1)*:3
plus radiation therapy for squamous cell carcinoma of the lung, *4(2)*:157
new agents in the treatment of bronchogenic carcinoma, *4(2)*:227
nitroscureas
plus other agents in advanced gastrointestinal cancer, *4(3)*:27
plus other agents in several tumors, *4(3)*:35
plasmacytoma, guidelines for, *4(1)*:145
radiation therapy
plus atmospheric oxygen and 5-fluorouracil in the treatment of lung cancer, *4(2)*:165
plus chemotherapy for small cell carcinoma of the lung, *4(2)*:171
remission rates, survival, and prognostic factors for bronchogenic carcinoma, *4(2)*:199
reports on various agents, *3(1)*:73
RSV after pulmonary resection for bronchogenic carcinoma, *4(2)*:261
surgery
adjuvant chemotherapy in the treatment of bronchial carcinoma, *4(2)*:119
adjuvant studies in lung cancer, *4(2)*:109
plus other treatments for lung cancer, *4(2)*:19
plus radiotherapy or chemotherapy in the treatment of lung cancer, *4(2)*:133
treatment of bronchogenic carcinoma, *4(2)*:207
treatment of lung cancer, National Cancer Institute of Milan, *4(2)*:231
treatment of squamous cell lung cancer, *6(2)*:361
vincristine plus adriamycin and methotrexate in patients with disseminated cancer, *6(2)*:339
Clinical studies: single agents
adriamycin
activity in genitourinary and gynecologic malignancies, *6(2)*:297
against various tumors, *4(3)*:47
arterial infusion of, *6(2)*:187
cardiomyopathy, an overview with determination of risk factors, *6(2)*:195
cardiomyopathy in, *6(2)*:203
cardiotoxicity: a clinicopathologic correlation, *6(2)*:215
cardiotoxicity in children, *6(2)*:209
clinical pharmacology, *6(2)*:183
DNA-adriamycin complex in clinical trials, *6(2)*:131
in pediatric malignancies, *6(2)*:259
phase II study in childhood solid tumors, *6(2)*:267
response of bronchogenic carcinoma, *6(2)*:349
studies at the Istituto Nazionale Tumori, Milan, *6(2)*:231
toxicology, a practical approach, *6(2)*:191
treatment of advanced breast cancer, *6(2)*:329
treatment of breast cancer: overview of studies, *6(2)*:319
treatment of bronchogenic carcinoma, *6(2)*:353
treatment of lung cancer, European studies, *6(2)*:343
treatment of lymphomas, *6(2)*:375
treatment of osteosarcoma, *6(2)*:305
treatment of soft tissue and bony sarcomas, *6(2)*:271
treatment of thyroid carcinoma, *6(2)*:283
treatment of various tumors, *3(1)*:33, *6(2)*:389
treatment of various tumors in the United States, *6(2)*:247
azotomycin in the treatment of various tumors, *1(1)*:207
BCNU in the treatment of various tumors, *1(1)*:115
BIC in the treatment of various tumors, *1(1)*:63, *3(1)*:33
bleomycin marked with radioactive isotopes in cancer treatment, *4(2)*:245
CCNU in the treatment of various tumors, *1(1)*:115, *3(1)*:33
cyclophosphamide, in lung cancer, *4(2)*:215
cytosine arabinoside in the treatment of various tumors, *1(1)*:179
dibromodulcitol in the treatment of various tumors, *1(1)*:165
leukemia, chronic granulocytic, guidelines for, *4(1)*:167
leukemia, chronic lymphocytic, guidelines for, *4(1)*:159
methods of study, *2(1)*:81
methotrexate
high-dose, pharmacokinetics, *6(1)*:19
high-dose, clinical pharmacology, *6(1)*:25
in clinical trials, *6(1)*:1
methyl-CCNU treatment of bronchogenic carcinoma, *4(2)*:257
mitomycin C in the treatment of various tumors, *1(1)*:99
new drugs available for bronchogenic carcinoma, *4(2)*:265
nitrosoureas
in advanced intestinal cancer, *4(3)*:27
in brain tumors, *4(3)*:21
in several tumors, *4(3)*:35
phase II study of various agents, particularly concerning disseminated breast cancer, *3(1)*:29
plasmacytoma, guidelines for, *4(1)*:145
porfiromycin in the treatment of various tumors, *1(1)*:81
quantitative relationships between toxic doses of antitumor chemotherapeutic agents in animals and man, *3(1)*:13
reports on various agents, *3(1)*:73
tabular analysis of the clinical chemotherapy of solid tumors, *6(2)*:399
treatment of bronchogenic carcinoma, *4(2)*:31,177

treatment of lung cancer, National Cancer Institute of Milan, *4(2)*:231
treatment of lung cancer, USSR, *4(2)*:251
Computers, simulation study of the preclinical development of anticancer drugs, *5(1)*:65
Contracts, at the National Cancer Institute, *4(3)*:73
Cyclophosphamide (NSC–26271)
after radical resection in bronchogenic carcinoma, *4(2)*:125
in preclinical and clinical trials, *4(2)*:265
plus adriamycin, melphalan, and vincristine in primary treatment of osteogenic sarcoma, *6(2)*:315
plus radiation therapy for oat cell carcinoma of the lung, *4(2)*:159
plus radiotherapy for unresectable bronchogenic carcinoma, *4(2)*:161
single-dose toxicity in dogs and monkeys, *4(1)*:51
standard for trial of new drugs in lung cancer, *4(2)*:215
Cytosine arabinoside (NSC–63878)
clinical brochure, *1(1)*:179
pharmacology report, *3(1)*:69
pharmacokinetics in animals and man, *3(1)*:21

D

Daunomycin *see* Daunorubicin
Daunorubicin (NSC–82151)
adriamycin and some structural analogs: macromolecular interactions and their biologic consequences, *6(2)*:115
cell interactions: determinants of selective toxicity of adriamycin and, *6(2)*:107
compared with adriamycin against L1210 leukemia, *3(1)*:33
compared with adriamycin: mode and mechanism of action, *6(2)*:91
Dehydroepiandrosterone mustard (NSC–121210), toxicity in beagle dogs, *4(1)*:85
α-2′-Deoxythioguanosine (NSC–71851), preclinical toxicology of, *5(1)*:9
Dibromodulcitol (NSC–104800), clinical brochure, *1(1)*:165
***cis*-Dichlorodiammineplatinum(II) (NSC–119875)**, in preclinical and clinical trials, *4(2)*:265
Dihydrofolate reductase, analysis of the cytotoxic determinants for methotrexate: a role for "free" intracellular drug, *6(1)*:51
DNA-adriamycin complex: preliminary results in mice and man, *6(2)*:131
Dogs
actinomycin D preclinical toxicology, *4(1)*:77
2,2′-(9,10-anthrylenedimethylene)bis[2-thiopseudourea], dihydrochloride, dihydrate toxicity, *1(1)*:153
azotomycin toxicity studies, *1(1)*:207
BCNU and CCNU toxicity, *1(1)*:115
BIC toxicity, *1(1)*:63
camptothecin toxicity, *5(1)*:25
CCNU preclinical toxicologic evaluation of single iv infusion, *5(1)*:53
cyclophosphamide single-dose toxicity, *4(1)*:51
dibromodulcitol toxicity studies, *1(1)*:165
estradiol mustard toxicity, *4(1)*:121
laboratory of toxicology, *2(1)*:61
mitomycin C toxicity, *1(1)*:99
neocarzinostatin toxicity studies, *5(1)*:43
phenesterin, estradiol mustard, and dehydroepiandrosterone mustard toxicity, *4(1)*:85
phenesterin toxicologic studies, *4(1)*:103
2,5-piperazinedione, 3,6-bis(5-chloro-2-piperidyl)-, dihydrochloride toxicity studies, *5(1)*:37
preclinical evaluation of tetrahydrouridine, *5(1)*:15
preclinical toxicology of α-2′-deoxythioguanosine, *5(1)*:9
preclinical toxicology trials with ICRF–159, *5(1)*:1
procarbazine toxicologic study, *4(1)*:97
quantitative relationships between toxic doses of antitumor chemotherapeutic agents in animals and man, *3(1)*:13
d-tetrandrine toxicology studies, *5(1)*:79
β-thioguanine deoxyriboside preclinical toxicologic studies, *4(1)*:41
toxicology and pharmacology of the nitrosoureas, *4(3)*:13
toxicology protocols, *4(1)*:1
vincristine toxicologic studies using iv injection, *5(1)*:17
Dosage schedule *see* Treatment schedule
Dosage selection, in screening protocols, *3(2)*:25
Dose formulation, report on, *3(1)*:77
Drug Research and Development (DR&D)
interpretation chart for coding used in screening data summaries, *3(2)*:69
pharmacology in the program of the National Cancer Institute, *2(1)*:73
summary of the usual characteristics of test systems used in the past under the auspices of the DR&D, *3(2)*:87
Drug screening
history and summary, *2(1)*:3
in vivo-in vitro experiments in, *3(1)*:57
interpretation chart for coding used in DR&D data summaries, *3(2)*:69
Laboratory of Toxicology, *3(1)*:61
molecular control program, *4(3)*:79
procedures for preclinical toxicologic evaluation of cancer chemotherapeutic agents, *4(1)*:1
protocols, *3(2)*:1
selection of agents, *2(1)*:9
test evaluation, *3(2)*:47
testing procedures, *3(2)*:41
testing schema for primary screening, *3(2)*:53
DTIC (NSC–45388), clinical brochure, *1(1)*:63

E

Ellipticine (NSC–71795), pharmacology report, *3(1)*:69
Estradiol mustard (NSC–112259)
clinical brochure, *4(1)*:121
toxicity in beagle dogs, *4(1)*:85
Ewing's sarcoma *see* Sarcoma, Ewing's

F

First International Workshop for Therapy of Lung Cancer, *4(2)*:5
5-Fluorouracil (NSC–19893)
  phase II study in disseminated breast cancer, *3(1)*:29
  plus radiotherapy and atmospheric oxygen in the treatment of lung cancer, *4(2)*:165
Folic acids, membrane transport of methotrexate and other folic acids, relevance to rescue protocols, *6(1)*:63

G

Gastrointestinal cancer *see* Carcinoma in man, gastrointestinal
Genitourinary cancer *see* Carcinoma in man, genitourinary
Germ-free biology, and the patient with malignant disease: clinical and preclinical studies, *4(3)*:61
Guanazole (NSC–1895), treatment of L1210 leukemia, *3(1)*:33
Guidelines for research *see* Protocols in drug screening and evaluation
Guinea pigs, 2,2-(9,10-anthrylenedimethylene)bis[2-thiopseudourea], dihydrochloride, dihydrate, toxicity, *1(1)*:153
Gynecologic cancer *see* Carcinoma in man, gynecologic

H

Hamsters, adriamycin, pathologic effects of, *6(2)*:159
Hepatoblastoma *see* Carcinoma in man, liver
Histology
  correlation with cell kinetic studies in lung cancer, *4(2)*:69
  epidemiology of different types of bronchogenic carcinoma, *4(2)*:59
  malignancy-associated changes in oral and bronchial epithelial cells in sputum specimens, *4(2)*:73
  reliability of diagnosis in lung cancer, *4(2)*:79
  squamous metaplasia and squamous cell carcinoma of the respiratory epithelium in hamsters, *4(2)*:43
Hodgkin's disease
  advanced, treatment with BCNU plus other agents, *3(1)*:33
  treatment with adriamycin, *6(2)*:375
  treatment with BCNU, CCNU, or methyl-CCNU alone or in combination with other agents, *4(3)*:35

I

ICRF–159 (NSC–129943)
  plus radiotherapy in bronchogenic carcinoma, *4(2)*:243
  preclinical toxicology studies with, *5(1)*:1
  treatment of L1210 leukemia, *3(1)*:33
Immunity, cell-mediated, in lung cancer patients: data, problems, and propositions, *4(2)*:279
Immunology
  of lung cancer, *4(2)*:29
  status before and during immunotherapy (immune profile), *4(2)*:275
Immunotherapy
  after incomplete resection for bronchogenic carcinoma, *4(2)*:293
  "immune" RNA—a new model, *4(2)*:287
  immunologic status before and during, immune profile, *4(2)*:275
  nonspecific for lung cancer, *4(2)*:283
  of lung cancer, *4(2)*:28,271
International Union Against Cancer program, *4(2)*:9
Isophosphamide (NSC–109724), in preclinical and clinical trials, *4(2)*:265

L

L5178Y *see* Tumor systems in animals, lymphoma, L5178Y
Laboratory of Toxicology *see* Toxicology, Laboratory of
Leukemia in man
  acute
    adriamycin treatment, *6(2)*:389
    childhood
      cytosine arabinoside in the treatment of, *1(1)*:179
      methotrexate, high-dose plus citrovorum factor rescue, *6(1)*:3
    cytosine arabinoside in the treatment of, *1(1)*:179
    lymphocytic
      adriamycin treatment, *6(2)*:369
      membrane transport of methotrexate, *6(1)*:73
    myelocytic, adult, membrane transport of methotrexate, *6(1)*:73
    nonlymphocytic, adriamycin treatment, *6(2)*:369
  chronic
    granulocytic, proposed guidelines for protocol studies, *1(1)*:53, *4(1)*:167
    lymphocytic, proposed guidelines for protocol studies, *1(1)*:41, *4(1)*:159
    myelogenous, dibromodulcitol treatment in, *1(1)*:165
Lewis lung carcinoma *see* Tumor systems in animals, carcinoma, Lewis lung
L1210 leukemia *see* Tumor systems in animals, L1210 leukemia
Linear array *see* Protocols for drug screening and evaluation
Liver cancer *see* Carcinoma in man, liver
Lung cancer *see* Carcinoma in man, lung
Lymphoma
  adriamycin treatment, *6(2)*:369
  malignant, combination usage of adriamycin, *6(2)*:381
  spontaneous AK leukemia (lymphoma) as a model for human, *3(1)*:3
  treatment with adriamycin, *6(2)*:375

M

Melphalan (NSC–8806), plus adriamycin, vincristine, and cyclophosphamide in primary treatment of osteogenic sarcoma, *6(2)*:315

Membrane transport
of methotrexate and other folate compounds: relevance to rescue protocols, *6(1)*:63
of methotrexate in human neoplastic tissue, *6(1)*:73
Metastasis
frequency after surgical resection for lung cancer, *4(2)*:63
of lung cancer, *4(2)*:303
should initial treatment of small cell carcinoma include systemic chemotherapy and brain irradiation?, *4(2)*:239
Mechlorethamine (NSC–762), plus other agents in squamous cell lung cancer, *6(2)*:361
Methotrexate (NSC–740)
analysis of the cytotoxic determinants of: a role for "free" intracellular drug, *6(1)*:51
citrovorum factor for high-dose, overview of protocols on clinical studies, *6(1)*:7
citrovorum factor rescue for high-dose: background and rationale, *6(1)*:3
citrovorum factor rescue for high-dose, for children with osteosarcoma and other malignant tumors, *6(1)*:13
high-dose, pharmacokinetics, *6(1)*:19
high-dose, clinical pharmacology, *6(1)*:25
high-dose plus citrovorum factor, clinical trial of, toxicologic and therapeutic observations, *6(1)*:43
high-dose plus citrovorum factor, toxicity of, in osteogenic sarcoma, *6(1)*:31
membrane transport of, other folate compounds: relevance to rescue protocols, *6(1)*:63
membrane transport of, in human neoplastic tissue, *6(1)*:73
perspectives on high-dose therapy, *6(1)*:1
plus adriamycin and vincristine in patients with disseminated breast cancer, *6(2)*:339
plus adriamycin in patients with disseminated breast cancer, *6(2)*:335
plus L-asparaginase, improvement in the therapeutic index of, *6(1)*:37
plus radiation therapy for squamous cell carcinoma of the lung, *4(2)*:157
Methyl-CCNU (NSC–95441)
alone or combined with other agents in advanced gastrointestinal cancer, *4(3)*:27
formulation for iv use, *4(3)*:7
phase II study on bronchogenic carcinoma, *4(2)*:257
toxicology and pharmacology, *4(3)*:13
treatment of brain tumors, *4(3)*:21
treatment of several tumors, *4(3)*:35
Mice
adriamycin, pathologic effects of, *6(2)*:159
adriamycin, toxicity studies of, *6(2)*:137
2,2′-(9,10-anthrylenedimethylene)bis[2-thiopseudourea], dihydrochloride, dihydrate, toxicity, *1(1)*:153
azotomycin toxicity studies, *1(1)*:207
BCNU and CCNU toxicity, *1(1)*:115
BIC toxicity, *1(1)*:63
camptothecin toxicity, *5(1)*:25
determinants of selective toxicity of adriamycin and daunorubicin, *6(2)*:107
dibromodulcitol toxicity studies, *1(1)*:165
DNA-adriamycin complex: toxicity studies, *6(2)*:131
pharmacokinetics, compared to man, *3(1)*:21
quantitative relationships between toxic doses of antitumor chemotherapeutic agents in animals and man, *3(1)*:13
β-thioguanine deoxyriboside, preclinical toxicologic studies, *4(1)*:41
toxicology and pharmacology of the nitrosoureas, *4(3)*:13
toxicology protocols, *4(1)*:1
Mitomycin C (NSC–26980)
clinical brochure, *1(1)*:99
phase II study in disseminated breast cancer, *3(1)*:29
Model systems
cell kinetics and the chemotherapy of cancer, *2(1)*:23
"immune" RNA in the immunotherapy of cancer, *4(2)*:287
in vitro phase-specificity screening, *3(1)*:7
in vivo-in vitro screening, *3(1)*:57
pharmacokinetics, *3(1)*:21
pharmacology in the chemotherapy drug development program of the National Cancer Institute, *2(1)*:73
rationale of combination chemotherapy based on preclinical experiments, *4(2)*:189
simulation study of the preclinical development of anticancer drugs, *5(1)*:65
spontaneous AK leukemia (lymphoma) as a model for human leukemias and lymphomas, *3(1)*:3
summary of the usual systems used in the past under the auspices of the DR&D, *3(2)*:87
Moloney sarcoma *see* Tumor systems in animals, sarcoma, Moloney virus-induced
Monkeys
adriamycin, pathologic effects of, *6(2)*:159
2,2′-(9,10-anthrylenedimethylene)bis[2-thiopseudourea], dihydrochloride, dihydrate toxicity, *1(1)*:153
bleomycin preclinical toxicology evaluation, *4(1)*:31
BCNU and CCNU toxicity, *1(1)*:115
camptothecin toxicity, *5(1)*:25
CCNU preclinical toxicologic evaluation of single iv infusion, *5(1)*:53
cyclophosphamide single-dose toxicity, *4(1)*:51
dibromodulcitol toxicity studies, *1(1)*:165
Laboratory of Toxicology, *2(1)*:61
mitomycin C toxicity, *1(1)*:99
phenesterin toxicologic studies, *4(1)*:103
2,5-piperazinedione, 3,6-bis(5-chloro-2-piperidyl)-, dihydrochloride toxicity studies, *5(1)*:37
preclinical toxicology of α-2′-deoxythioguanosine, *5(1)*:9
preclinical toxicology of tetrahydrouridine, *5(1)*:15
preclinical toxicology trials with ICRF–159, *5(1)*:1
procarbazine toxicologic study, *4(1)*:97
d-tetrandrine toxicology studies, *5(1)*:79
toxicology and pharmacology of the nitrosoureas, *4(3)*:13
toxicology protocols, *4(1)*:1
vincristine toxicologic evaluation using iv injections, *5(1)*:17
Multiple myeloma *see* Myeloma, multiple
Myeloma, multiple, adriamycin treatment, *6(2)*:369
Myelosuppressive patients, obstacles to routine transfusion support, *4(3)*:51

N

National Cancer Institute, NIH
contracts at, *4(3)*:73
pharmacology in the chemotherapy drug development program, *2(1)*:73
National Cancer Institute of Milan
adriamycin studies, *6(2)*:231
chemotherapy of lung cancer, *4(2)*:231
treatment of bronchogenic carcinoma with surgery and radiotherapy, *4(2)*:101
Natural products, as anticancer agents, *3(1)*:55
Neocarzinostatin (NSC–69856), toxicity evaluation in dogs, an antitumor antibiotic with radiomimetic and antigenic characteristics, *5(1)*:43
Neuroblastoma, childhood, adriamycin phase II study, *6(2)*:267
Nitrosourea compounds
alone or combined with other agents in advanced gastrointestinal cancer, *4(3)*:27
alone or in combination against several tumors, *4(3)*:35
formulation for iv use, *4(3)*:7
historical development and future promise as anticancer agents, *4(3)*:3
toxicology and pharmacology, *4(3)*:13
treatment of brain tumors, *4(3)*:21
NSC–740 *see* Methotrexate
NSC–762 *see* Mechlorethamine
NSC–1895 *see* Guanazole
NSC–3053 *see* Actinomycin D
NSC–3590 *see* Citrovorum factor
NSC–8806 *see* Melphalan
NSC–19893 *see* 5-Fluorouracil
NSC–26271 *see* Cyclophosphamide
NSC–26980 *see* Mitomycin C
NSC–45388 *see* DTIC
NSC–56054 *see* 2,2′-(9,10-Anthrylenedimethylene)bis[2-thiopseudourea], dihydrochloride, dihydrate
NSC–56410 *see* Porfiromycin
NSC–56654 *see* Azotomycin
NSC–58514 *see* Chromomycin A_3
NSC–63878 *see* Cytosine arabinoside
NSC–67574 *see* Vincristine
NSC–69856 *see* Neocarzinostatin
NSC–71261 *see* β-Thioguanine deoxyriboside
NSC–71795 *see* Ellipticine
NSC–71851 *see* α-2′-Deoxythioguanosine
NSC–77037 *see* *d*-Tetrandrine
NSC–77213 *see* Procarbazine
NSC–79037 *see* CCNU
NSC–82151 *see* Daunorubicin
NSC–82196 *see* BIC
NSC–95441 *see* Methyl-CCNU
NSC–100880 *see* Camptothecin
NSC–102816 *see* 5-Azacytidine
NSC–104469 *see* Phenesterin
NSC–104800 *see* Dibromodulcitol
NSC–109229 *see* L-Asparaginase
NSC–109724 *see* Isophosphamide
NSC–112259 *see* Estradiol mustard
NSC–112907 *see* Tetrahydrouridine
NSC–119875 *see* *cis*-Dichlorodiammineplatinum(II)
NSC–121210 *see* Dehydroepiandrosterone mustard
NSC–123127 *see* Adriamycin
NSC–125066 *see* Bleomycin
NSC–129943 *see* ICRF–159
NSC–135758 *see* 2,5-Piperazinedione, 3,6-bis(5-chloro-2-piperidyl),- dihydrochloride
NSC–409962 *see* BCNU

O

Oat cell carcinoma *see* Carcinoma in man, lung, oat cell
Osteosarcoma *see* Sarcoma, osteogenic
Ovarian tumor *see* Carcinoma in man, ovary
Oxygen, atmospheric, plus radiotherapy and 5-fluorouracil in the treatment of lung cancer, *4(2)*:165

P

P288 *see* Cell line, lymphoma P288 or Tumor systems in animals, P288 lymphoma
P388 *see* Tumor systems in animals, P388 leukemia
Pharmacokinetics, using cytosine arabinoside as an example, *3(1)*:21
Pharmacology, working session report, *3(1)*:69
Phase I studies
adriamycin cardiotoxicity: a clinicopathologic correlation, *6(2)*:215
adriamycin in patients with osteosarcoma, *6(2)*:305
azotomycin in the treatment of various tumors, *1(1)*:207
CCNU treatment of various tumors, *3(1)*:33
clinical trials and combination chemotherapy, *2(1)*:81
DNA-adriamycin complex in clinical trials, *6(2)*:131
lung cancer chemotherapy, *4(2)*:25
new agents and combinations in the treatment of bronchogenic carcinoma, *4(2)*:227
new drugs available for study, *4(2)*:265
nitrosoureas against several tumors, *4(3)*:35
treatment of lung cancer, National Cancer Institute of Milan, *4(2)*:231
Phase II studies
adriamycin in childhood solid tumors, *6(2)*:267
adriamycin in patients with osteosarcoma, *6(2)*:305
adriamycin treatment of various tumors, *6(2)*:389
clinical trials and combination chemotherapy, *2(1)*:81
lung cancer chemotherapy, *4(2)*:25
methyl-CCNU treatment of bronchogenic carcinoma, *4(2)*:257
new agents and combinations in the treatment of bronchogenic carcinoma, *4(2)*:227
new drugs available for study, *4(2)*:265
nitrosoureas in several tumors, *4(3)*:35
reflections, particularly concerning disseminated breast cancer, *3(1)*:29
treatment of bronchogenic carcinoma, *4(2)*:31
treatment of lung cancer, *4(2)*:215
treatment of lung cancer, National Cancer Institute of Milan, *4(2)*:231

Phase III studies
clinical trials and combination chemotherapy, *2(1)*:81
lung cancer chemotherapy, *4(2)*:25
nitrosoureas in several tumors, *4(3)*:35
Phenesterin (NSC-104469)
clinical brochure, *4(1)*:103
toxicity in beagle dogs, *4(1)*:85
Photofluorographic detection, of primary lung cancer, survival factors, *4(2)*:95
2,5-Piperazinedione, 3,6-bis(5-chloro-2-piperidyl),- dihydrochloride (NSC-13578), toxicologic evaluation in dogs and monkeys, *5(1)*:37
Plant alkaloids, *d*-tetrandrine, toxicology studies in dogs and monkeys, *5(1)*:79
Plasma cell cytoma *see* Plasmacytoma
Plasmacytoma, proposed guidelines for protocol studies, *1(1)*:17, *4(1)*:145
Platelets *see* Blood platelets
Porfiromycin (NSC-56410), clinical brochure, *1(1)*:81
Procarbazine (NSC-77213), preclinical toxicologic study, *4(1)*:97
Propagation of tumor lines, *3(2)*:29
Protocols in drug screening and evaluation
adriamycin activity in genitourinary and gynecologic malignancies, *6(2)*:297
adriamycin studies, *6(2)*:231
animals and animal care, *3(2)*:37
B16 melanoma, melanotic, *3(2)*:11
cell culture technical procedures, *3(2)*:59
clinical trials and combination chemotherapy, *2(1)*:81
combination usage of adriamycin in malignant lymphomas, *6(2)*:381
general instructions, *3(2)*:19
International Union Against Cancer, *4(2)*:9
interpretation chart for coding used in DR&D screening data summaries, *3(2)*:69
Laboratory of Toxicology, *2(1)*:61
KB cell culture screen, *3(2)*:17
leukemia, chronic granulocytic, guidelines for studies, *4(1)*:167
leukemia, chronic granulocytic, proposed guidelines for new agents in the treatment of, *1(1)*:53
leukemia, chronic lymphocytic, guidelines for study, *4(1)*:159
leukemia, chronic lymphocytic, proposed guidelines for study, *1(1)*:41
Lewis lung carcinoma, *3(2)*:13
L1210 leukemia, lymphoid, *3(2)*:7
membrane transport of methotrexate and other folate compounds: relevance to rescue, *6(1)*:63
methotrexate, high-dose, with citrovorum factor rescue, overview of clinical studies, *6(1)*:7
nitrosoureas in various tumors, *4(3)*:35
P388 leukemia, lymphocytic, *3(2)*:9
plasmacytoma, guidelines for studies, *4(1)*:145
plasmacytoma, proposed guidelines for studies, *1(1)*:17
preclinical toxicologic evaluation of cancer chemotherapeutic agents, *4(1)*:1
preparation and administration of test materials, *3(2)*:21
propagation of tumor lines, *3(2)*:29
randomization of animals, *3(2)*:45
screening antineoplastic agents against animal tumors and other biologic systems, *3(2)*:1
selection of agents for the tumor screen, *2(1)*:9
selection of dosages, *3(2)*:25
simulation study of the preclinical development of anticancer drugs, *5(1)*:65
summary of the usual characteristics of test systems used in the past under the auspices of the DR&D, *3(2)*:87
test evaluation, *3(2)*:47
testing procedures, *3(2)*:41
testing schema for primary screening, *3(2)*:53
tumor quality control, *3(2)*:33
tumor transplantation, *3(2)*:31
Walker 256 carcinosarcoma, *3(2)*:15

R

Rabbits
adriamycin, pathologic effects of, *6(2)*:159
adriamycin pharmacology in, *6(2)*:153
adriamycin toxicity in, *6(2)*:177
2,2′-(9,10-anthrylenedimethylene)bis[2-thiopseudourea], dihydrochloride, dihydrate, toxicity, *1(1)*:153
Radiation therapy
alone or plus ICRF-159 in bronchogenic carcinoma, *4(2)*:243
alone or with atmospheric oxygen and 5-fluorouracil in the treatment of lung cancer, *4(2)*:165
brain, plus chemotherapy for small cell carcinoma, *4(2)*:239
for bronchogenic carcinoma, National Cancer Institute of Milan, *4(2)*:101
for lung cancer, *4(2)*:311
plus adriamycin in pediatric malignancies, *6(2)*:259
plus cyclophosphamide for oat cell carcinoma of the lung, *4(2)*:159
plus cyclophosphamide for unresectable bronchogenic carcinoma, *4(2)*:161
plus methotrexate for squamous cell carcinoma of the lung, *4(2)*:157
plus surgery in the treatment of lung cancer, *4(2)*:133
plus various chemotherapeutic agents for small cell carcinoma of the lung, *4(2)*:171
techniques suitable for intercenter cooperative studies of bronchogenic carcinoma, *4(2)*:137
treatment of bronchogenic carcinoma, *4(2)*:153
treatment of lung cancer, *4(2)*:145
Radioactive isotopes, as markers for chemotherapeutic drugs, *4(2)*:245
Rats
adriamycin, pathologic effects of, *6(2)*:159
adriamycin toxicity in, *6(2)*:177
azotomycin toxicity studies, *1(1)*:207
BCNU and CCNU toxicity, *1(1)*:115
BIC, toxicity, *1(1)*:63
camptothecin toxicity, *5(1)*:25
Laboratory of Toxicology, *2(1)*:61
mitomycin C toxicity, *1(1)*:99
phenesterin toxicologic studies, *4(1)*:103

quantitative relationships between toxic doses of antitumor chemotherapeutic agents in animals and man, *3(1)*:13
Rhabdomyosarcoma
adriamycin in pediatric malignancies, *6(2)*:259
childhood, adriamycin phase II study, *6(2)*:267
Ridgway osteogenic sarcoma *see* Tumor systems in animals, sarcoma, Ridgway osteogenic
RNA, "immune"—a new model for the immunotherapy of cancer, *4(2)*:287
RSV, after pulmonary resection for bronchogenic carcinoma, *4(2)*:261

S

Sarcoma
adriamycin treatment, *6(2)*:389
Ewing's
adriamycin in pediatric malignancies, *6(2)*:259
childhood, adriamycin phase II study, *6(2)*:267
osteogenic
adriamycin in pediatric malignancies, *6(2)*:259
adriamycin treatment in, *6(2)*:305
childhood, adriamycin phase II study, *6(2)*:267
methotrexate, high-dose, toxicity of, plus citrovorum factor, *6(1)*:31
methotrexate, high-dose with citrovorum factor rescue: response, toxicity, and pharmacokinetics, *6(1)*:13
primary treatment with adriamycin and other agents, *6(2)*:315
soft tissue and bony, adriamycin used alone and in combination, *6(2)*:271
Scheduling *see* Treatment schedule
Small cell carcinoma *see* Carcinoma in man, lung, small cell
Solid tumors, tabular analysis of chemotherapy for, *6(2)*:399
Sputum specimens, malignancy-associated changes in oral and bronchial epithelial cells, *4(2)*:73
Squamous cell carcinoma *see* Carcinoma in man, lung, squamous cell
Statistics
data retrieval in bronchogenic carcinoma, *4(2)*:31
interdisciplinary group on clinical trials, *4(2)*:317
Structure-activity relationship
adriamycin: new chemical developments and analogs, *6(2)*:123
BCNU and CCNU: clinical brochure, *1(1)*:115
daunorubicin, adriamycin, and some structural analogs: macromolecular interactions and their biologic consequences, *6(2)*:115
dibromodulcitol and analogs, *1(1)*:165
formulation of three nitrosoureas for iv use, *4(3)*:7
selection of agents for the tumor screen, *2(1)*:9
synthetic chemistry, *3(1)*:49
toxicology and pharmacology of the nitrosoureas, *4(3)*:13
Supportive care, in cancer therapy, *2(1)*:99
Surgery
adjuvant chemotherapy in the treatment of bronchial carcinoma, *4(2)*:119
adjuvant studies in lung cancer, *4(2)*:109
adriamycin in pediatric malignancies, *6(2)*:259
frequency of residual and metastatic tumor after curative resection for lung cancer, *4(2)*:63
in bronchogenic carcinoma, National Cancer Institute of Milan, *4(2)*:101
in lung cancer, comparative results of right pneumonectomy and sleeve lobectomy, *4(2)*:97
plus cyclophosphamide for radically resected bronchogenic carcinoma, *4(2)*:125
plus radiotherapy or chemotherapy in the treatment of lung cancer, *4(2)*:133
pulmonary resection with or without RSV for bronchogenic carcinoma, *4(2)*:261
resection, incomplete followed by immunotherapy for bronchogenic carcinoma, *4(2)*:293
surgeon's viewpoint on collaborative research on lung cancer, *4(2)*:307
treatment for lung cancer, prospects and priorities for clinical research, *4(2)*:19
Synthetic chemistry, in the design of anticancer agents, *3(1)*:49

T

Tabular analysis of the clinical chemotherapy of solid tumors, *6(2)*:399
Tetrahydrouridine (NSC–112907), preclinical toxicology in dogs and monkeys, *5(1)*:15
***d*-Tetrandrine (NSC–77037)**, toxicology studies with, a plant alkaloid with vascular and lymphotoxic effects in dogs and monkeys, *5(1)*:79
β-Thioguanine deoxyriboside (NSC–71261), preclinical toxicologic studies, *4(1)*:41
Thyroid carcinoma *see* Carcinoma in man, thyroid gland
Toxicity studies in man *see* Clinical studies: single agents or combination of agents
Toxicology, Laboratory of
procedures for preclinical toxicologic evaluation of cancer chemotherapeutic agents, *4(1)*:1
protocols of clinical studies designed by, *2(1)*:61
working session report, *3(1)*:63
Treatment schedule
2,2′-(9,10-anthrylenedimethylene)bis[2-thiopseudourea], dihydrochloride, dihydrate in various tumors, *1(1)*:153
BCNU and CCNU against L1210 leukemia, *1(1)*:115
cytosine arabinoside in animal and human tumors, *1(1)*:179
dependency of experimentally active antileukemic (L1210) drugs, *2(1)*:35
dibromodulcitol in various tumors, *1(1)*:165
DTIC, against various tumors, *1(1)*:63
Laboratory of Toxicology report, *3(1)*:63
porfiromycin in clinical trials, *1(1)*:81
Tumor systems in animals
Adenocarcinoma 755, BIC treatment, *1(1)*:63
B16 melanoma
adriamycin activity in, *6(2)*:137
protocol for drug screening, *3(2)*:11

carcinoma, Lewis lung
chemotherapy in, *4(2)*:25
histogenesis of squamous metaplasia and squamous cell, in hamsters, *4(2)*:43
protocol for drug screening, *3(2)*:13
rationale of combination chemotherapy, *4(2)*:189
drug screening, *2(1)*:3
in vivo-in vitro screening, *3(1)*:57
leukemia
AKR
germ-free biology, *4(3)*:61
spontaneous, as a model for human leukemias and lymphomas, *3(1)*:3
estradiol mustard in, *4(1)*:121
L1210
adriamycin activity in, *6(2)*:137
adriamycin compared with daunorubicin in the treatment of, *3(1)*:33
2,2′-(9,10-anthrylenedimethylene)bis[2-thiopseudourea], dihydrochloride, dihydrate treatment, *1(1)*:153
azotomycin in the treatment of, *1(1)*:207
BCNU and CCNU treatment, *1(1)*:115
BIC treatment, *1(1)*:63
cytosine arabinoside in the treatment of, *1(1)*:179
dibromodulcitol treatment, *1(1)*:165
DNA-adriamycin in the treatment of, *6(2)*:131
guanazole treatment, *3(1)*:33
ICRF-159 in the treatment of, *3(1)*:33
new drugs available for study, *4(2)*:265
porfiromycin treatment of, *1(1)*:81
protocol for drug screening, *3(2)*:7
rationale of combination chemotherapy, *4(2)*:189
treatment schedule dependency of experimentally active antileukemic drugs, *2(1)*:35
treatment with natural products, *3(1)*:55
P388
adriamycin activity in, *6(2)*:137
protocol for drug screening, *3(2)*:9
treatment with natural products, *3(1)*:55
phenesterin activity in, *4(1)*:103
lymphoma
L5178Y, improvement in the therapeutic index of methotrexate by L-asparaginase, *6(1)*:37
P288, cell interactions, determinants of selective toxicity of adriamycin and daunorubicin, *6(2)*:107
mammary
estradiol mustard in, *4(1)*:121
phenesterin activity in, *4(1)*:103
mitomycin C treatment of, *1(1)*:99
quality control, *3(2)*:33
sarcoma
180 Crocker, BIC treatment, *1(1)*:63
Moloney, virus-induced, adriamycin activity in, *6(2)*:137
Ridgway osteogenic, adriamycin activity in, *6(2)*:137
Walker 256 carcinosarcoma
dibromodulcitol treatment, *1(1)*:165
BIC treatment, *1(1)*:63
protocol for drug screening, *3(2)*:15
Tumor transplantation, *3(2)*:31

U

USSR, chemotherapy of lung cancer, *4(2)*:251

V

Veterans' Administration, lung cancer therapy program, *4(2)*:7
Vincristine (NSC–67574)
plus adriamycin and methotrexate in patients with disseminated breast cancer, *6(2)*:339
plus adriamycin, melphalan, and cyclophosphamide in primary treatment of osteogenic sarcoma, *6(2)*:315
plus other agents in squamous cell lung cancer, *6(2)*:361
retrospective toxicologic evaluation in monkeys and dogs using weekly iv injections for 6 weeks, *5(1)*:17
Virology, in drug screening, *4(3)*:79

W

Walker 256 carcinosarcoma *see* Tumor systems in animals, Walker 256 carcinosarcoma
Wilms' tumor, childhood, adriamycin phase II study, *6(2)*:267

Author Index

A

Abbott BJ, *50*–659, *56*–483, *57*–501
Abeloff M, *58*–575
Aboul-Enein M, *59*–367
Abraham A, *51*–271
Abrams HL, *52*–81,157
Abul-Nasr AL, *57*–159
Ackerman C, *58*–421
Adams DF, *52*–81,157
Adamson RH, *52*–617, *55*–215, *56*–249, *58*–293,617, *59*–599
Adolphe AB, *59*–547
Ahluwalia BS, *59*–3
Ahmann DL, *56*–93,369,401, *57*–341, *58*–861,877, *59*–451,1103
Aisner J, *58*–927
Akiba T, *56*–9
Albala MM, *51*–81
Alberts DS, *59*–345
Albo V, *56*–523, *59*–351,989,1097
Alison RE, *54*–175
Allan BD, *58*–296, *59*–257
Allen LM, *56*–573,603,721, *57*–175, *59*–811,877
Al-Sarraf M, *56*–615
Ambrus JJ, *51*–253
Amick RM, *55*–83
Amo H, *56*–373
Anaclerio A, *58*–741
Anderson JB, *57*–125
Andrews CM, *56*–183
Andrews JR, *53*–313
Andrews NC, *50*–671, *51*–471, *52*–751, *54*–237, *55*–61,525, *58*–653
Andrysek O, *57*–311
Angelakis P, *53*–255
Ansfield FJ, *50*–671, *51*–167,189,483, *52*–263,297, *53*–243,249,287, *55*–61,183,205,259, *57*–59
Anton E, *50*–47
Apostol JV, *50*–573
Apple MA, *51*–455, *52*–687, *53*–195
Arduino LJ, *51*–295
Arena E, *59*–765
Arena PJ, *56*–207,779
Arima E, *57*–405
Ariyoshi Y, *56*–373
Arkun S, *58*–895
Armentrout SA, *56*–527, *58*–841
Armstrong JG, *50*–95, *52*–527
Aroesty J, *59*–861
Arseneau J, *53*–67
Arya SK, *59*–39
Asbell MA, *56*–315
Attah EB, *59*–3
Ausman RK, *50*–137, *52*–641,655,661,667,675
Aust JB, *50*–671, *51*–237
Avedon M, *58*–759
Avery TL, *57*–165, *59*–743

B

Babbitt HL, *51*–253
Babcock MS, *59*–59
Bachur NR, *54*–89, *59*–677,765
Baehner RL, *58*–671
Bagley CM, Jr, *56*–387
Bagshaw MA, *57*–473, *59*–165
Baguley BC, *55*–291
Bailar JC III, *50*–129
Bajetta E, *57*–429
Baker CG, *50*–349
Baker LH, *59*–1123
Balconi G, *57*–115
Baldini L, *53*–13
Balis ME, *53*–325
Ball CR, *59*–1083
Band PR, *57*–79, *59*–1139
Banerjee S, *55*–531, *56*–557
Baratta MC, *56*–483
Bardos TJ, *51*–253
Barker M, *51*–1,201, *58*–627
Barkley HT, Jr, *59*–377
Barlow JJ, *59*–1157
Barnard EA, *59*–97
Barnard S, *50*–47
Baronowsky PE, *52*–337
Bartholomew D, *53*–147
Barzi A, *59*–967
Bateman JR, *50*–675, *51*–25, *56*–263, *57*–477,481,497, *58*–249,723,947, *59*–1031,1177
Battle JD, *53*–71
Batz K, *59*–429
Baxter D, *55*–253
Bayard S, *58*–845
Bear JL, *59*–611,661
Beatty EC, Jr, *50*–339
Beckloff GL, *53*–385
Bellet RE, *56*–413, *57*–185, *58*–217, *59*–1181
Bender RA, *59*–795,805
Benjamin RS, *58*–271
Bennett JM, *59*–333
Berenbaum MC, *52*–539, *56*–563
Berenson MP, *55*–525
Bergevin PR, *57*–51,413
Bergsagel DE, *51*–378, *55*–175, *59*–537
Berman M, *59*–811

Bernstein I, *59*–1015
Bernstein JG, *54*–89
Berry DH, *52*–441,631
Bertino JR, *51*–69,305, *55*–607, *56*–201, *59*–523,575,1091
Bethune V, *58*–207
Beutler E, *53*–127
Bharagava A, *59*–97
Bhuyan BK, *56*–709, *58*–149,157
Bini A, *58*–325
Bischoff KB, *54*–95, *59*–777
Bisel HF, *50*–671, *51*–85, *52*–751, *55*–265, *56*–93,369, *58*–861,877, *59*–451
Blackard CE, *59*–225
Blackett NM, *59*–929
Blais M, *57*–187
Bleyer WA, *59*–721,795
Bloch A, *58*–471
Block GE, *58*–513
Block JB, *53*–3, *54*–461, *57*–373, *59*–985
Blom J, *55*–269, *56*–535,729, *57*–51,413
Bluming AZ, *59*–901
Bodey GP, *52*–315, *53*–59, *54*–131,255, *56*–543, *57*–219,319
Bogdon DL, *57*–481, *58*–947
Bohannon RA, *58*–947
Boileau G, *55*–595
Boldrey EB, *54*–273, *56*–421, *59*–327
Bollag W, *55*–53,59
Bonadonna G, *56*–343, *57*–429, *58*–251,365, *59*–1161
Bonar RA, *59*–51
Bonmassar E, *59*–967
Bonnet JD, *57*–231, *59*–425
Bono VH, *58*–793, *59*–481
Boone BA, *50*–543
Boone R, *50*–331
Boreham BA, *58*–189
Boronow RC, *53*–305
Borromeo RG, *53*–305
Borsa J, *58*–559
Bossi A, *57*–115
Boutis L, *57*–365
Bowen JM, *59*–17
Boxer GE, *50*–89
Brace K, *58*–401
Bradley RL, *58*–745
Bradner WT, *50*–79, *52*–389
Bradshaw JD, *56*–89
Braine H, *58*–375
Brambilla C, *58*–251
Brambilla G, *53*–13, *56*–579, *58*–633
Brandes D, *50*–47
Brändle E, *59*–707
Brannen GE, *59*–127
Braunwald J, *56*–263, *57*–481
Bray DA, *55*–215
Brazhnikova MG, *58*–255
Brema F, *59*–890
Bremner DN, *58*–889
Brenkus LB, *59*–847
Brenner L, *57*–11
Brescia T, Jr, *57*–149
Brewer CF, *58*–491
Brewin TB, *56*–83
Briggs R, *58*–697
Brindley CO, *50*–667
Britton HA, *58*–719
Brock N, *51*–315,341,379
Brockman H, *58*–9
Brockman RW, *54*–431, *55*–47, *56*–493
Broder LE, *59*–1001,1171
Brodovsky HS, *52*–315
Brook J, *55*–567,591
Broom AD, *53*–147
Bross IDJ, *50*–157, *52*–641,655,661, 667,675
Brown CH III, *54*–125
Brown DE, *54*–217
Brownlee RW, *52*–593, *57*–231,465
Brubaker C, *52*–321
Bruce WR, *58*–813, *59*–319
Bruckner HW, *59*–575
Brugarolas A, *56*–783, *59*–1025
Brunner KW, *55*–199, *59*–429
Buckner CD, *58*–697,709, *59*–1131
Bukva NF, *51*–431
Bull MI, *59*–1171
Bunn PA, Jr, *58*–127,620
Burchenal JH, *51*–435, *58*–207
Burdman J, *52*–509
Burgert EO, Jr, *56*–729
Burgess MA, *57*–319
Burke PJ, *52*–305
Burn JI, *58*–867
Burningham RA, *55*–199,269
Burns CP, *56*–527, *59*–757
Burns SL, *53*–153
Burrows JH, *52*–593, *54*–249
Buskirk HH, *50*–557, *56*–163,709
Byar D, *58*–845
Byfield JE, *57*–405, *58*–527
Byfield PE, *57*–405

C

Cahn EL, *51*–91
Cahow CE, *50*–327
Cain BF, *58*–189, *59*–679
Calabresi P, *57*–73
Calcagnino C, *58*–317
Call JB, *53*–211, *54*–461
Calveley SB, *58*–189
Canellos GP, *53*–67, *56*–387,611, *57*–361, *59*–599,893
Cangir A, *59*–371
Caoili EM, *59*–1117
Capizzi RL, *54*–191
Cappuccino JG, *53*–325
Caraceni CE, *56*–579
Carbone PP, *50*–95, *51*–91, *53*–67, *54*–125, *55*–159, *58*–689
Carey RW, *56*–729
Carpenter JT, *58*–753
Carr DT, *56*–401, *58*–913
Carrese LM, *50*–349
Carter AC, *55*–259

Carter CJK, *55*–539
Carter SK, *54*–295
Carter WA, *59*–39
Casazza AM, *56*–153, *57*–269
Casazza AR, *51*–91
Cathcart RT, *52*–99
Catherall EJ, *57*–263
Catsoulacos P, *57*–365
Cavanna M, *53*–13, *56*–579, *58*–633
Cavins JA, *51*–197
Cevik N, *50*–287
Chabner BA, *57*–361
Chadwick DP, *58*–171,637
Chadwick M, *58*–777
Chainuvati T, *59*–1167
Chalbaud RA, *59*–433
Chang H-Y, *59*–769
Chang IM, *59*–611
Chang P, *58*–927
Chao DL, *59*–661
Chapman JD, *58*–559
Chard RL, Jr, *58*–671
Chaube S, *51*–363, *53*–23
Chawla PL, *59*–389
Cheever MA, *59*–1131
Chen TT, *54*–9
Cheron R, *56*–1
Chia GA, *58*–919
Chignell CF, *57*–125
Children's Cancer Study Group A, *50*–337
Chirigos MA, *57*–305, *58*–821, *59*–531
Chmielewicz ZF, *51*–253
Choe B-K, *59*–147
Chu TM, *59*–97,195
Chuang S-N, *59*–827
Chung WS, *59*–1157
Churchhouse MJ, *58*–189
Ciaccio EI, *50*–89
Cioloca L, *57*–29
Clements D, *57*–325
Clifford GO, *52*–635
Clift RA, *58*–697,709
Cline MJ, *58*–521
Close HP, *54*–195,451
Cobb JP, *52*–543
Cobb LM, *54*–375, *58*–645
Cockburn A, *57*–263
Coffey DS, *59*–127,185
Coffey JJ, *56*–31
Cohen JL, *55*–253, *58*–723
Cohen MH, *56*–515, *58*–393,901, *59*–243,751,1001,1171
Cohen SM, *56*–751
Cohen SS, *59*–259
Cole DR, *56*–641
Cole GA, *54*–211
Cole MP, *56*–83
Coleman D, *59*–1131
Coleman GL, *59*–523, 1071
Coles DT, *56*–401, *58*–913
Colsky J, *51*–197,277,283, *52*–425, *58*–689, *59*–333
Coltman CA, Jr, *58*–213
Colvin M, *59*–411
Comis R, *55*–143,281
Connolly CA, *59*–3
Conzelman GM, Jr, *53*–105, *57*–235
Cooke WM, *58*–867
Cooney DA, *52*–563, *54*–217, *56*–611, *58*–793, *59*–481
Cooper MR, *57*–419
Cooper T, *55*–199, *56*–535
Copeland D, *58*–167
Copeland EM III, *59*–437
Cortes EP, *56*–237
Cortner JA, *52*–445
Costa J, *51*–235
Costachel O, *57*–29
Coune A, *59*–209
Courtenay VD, *59*–929
Cowan DH, *54*–175, *55*–175, *56*–357, *59*–537
Crafts D, *59*–327
Creasey WA, *52*–501, *54*–191
Creaven PJ, *56*–515,573,603,721, *57*–175, *58*–393,901, *59*–751,811,877,1001,1171
Cressy NL, *50*–683
Crim JA, *50*–577
Cronin AP, *50*–9
Crothers DM, *58*–97
Csuka O, *56*–593
Cunningham TJ, *52*–597, *53*–291, *58*–677, *59*–1127
Curran RE, *54*–103
Curtis JE, *58*–883, *59*–537
Cuttner J, *52*–445, *55*–199,269, *56*–729
Cysyk RL, *57*–291,299, *58*–298, *59*–685,689
Czajka DM, *50*–641

D

Danø K, *55*–133, *56*–321,701
Dao T, *58*–677
Darvey H, *58*–723
Das L, *58*–661
Das SK, *50*–331
Dasdia T, *57*–269, *58*–769
Davidson JP, *59*–287
Davis HL, Jr, *53*–243,249, *55*–183, *57*–59
Davis PJ, *58*–375
Davis RD, *52*–563
Decker DG, *51*–507, *57*–241
DeConti RC, *54*–191, *55*–599,607, *57*–201, *59*–1091
Dederick MM, *50*–259, *51*–231
Dedrick RL, *54*–95, *59*–795,805
De Fronzo RA, *58*–375
de Duve C, *59*–260
Degnan TJ, *56*–729
De Lena M, *56*–343, *58*–251
De Marsh Q, *59*–1131
Denham C, *55*–159
Dennis DL, *50*–255
de Palo GM, *57*–429
Desmond W, *59*–47
De Sombre ER, *58*–513
DeVita VT, Jr, *55*–159,215, *56*–249,387, *57*–361, *59*–1039

Devlin TM, *50*–89
DeWys WD, *52*–229, *57*–1,33,41, *59*–215
Diassi PA, *51*–225
Dickson JA, *58*–294
Didolkar MS, *58*–371
DiDomenico E, *59*–447
Dienstbier Z, *57*–311
Dietrich FS, *52*–603
Di Fronzo G, *52*–331
Di Marco A, *50*–659, *52*–331, *53*–33, *54*–1, *56*–153,431, *57*–269, *58*–769
Dinarello CA, *57*–393
Dines DE, *58*–913
Dion RL, *59*–481
Di Re F, *57*–429
Dittman W, *59*–1131
Dixon GJ, *50*–247,299, *51*–7, *52*–725
Dixon LM, *57*–185
Dmochowski L, *59*–17
Dobre V, *54*–319
Dobrow RB, *59*–1131
Dollinger MR, *51*–435
Dombernowsky P, *56*–71, *59*–1027
Donadio JV, Jr, *57*–341
Donaldson MH, *51*–399, *55*–67, *58*–683
Donati RM, *50*–649
Donavan MA, *59*–1127
Donelli MG, *54*–79, *57*–115
Donnenberg A, *58*–737
Double JA, *59*–1083
Douglass HO, Jr, *59*–1035
Downing V, *52*–611
Drewinko B, *59*–621,665
Dudrick SJ, *59*–437
Dulmadge EA, *50*–247, *51*–7, *52*–725, *56*–585
Durant J, *53*–131
Durie BGM, *58*–733
Dyment PG, *57*–335, *59*–359,371

E

Eagan RT, *58*–877,913, *59*–203,451
Eaves AC, *58*–813
Eckhardt S, *51*–261, *53*–377
Eckles N, *50*–271
Edlis H, *57*–11
Edmonson JH, *54*–245, *58*–877, *59*–451
Einhorn LH, *57*–437, *59*–769
Einstein AB, Jr, *59*–1131
El-Asfouri S, *59*–843
Elias EG, *56*–783
Ellison RR, *52*–425, *55*–199, *56*–237,535, *57*–485, *58*–233
El-Merzabani MM, *57*–159, *59*–367
El-Morsi B, *59*–367
Emanuel NM, *58*–135, *59*–888
Emlich CA, *58*–317
Emori M, *57*–85
Endicott KM, *50*–349
Engeler J, *59*–767
Engle R, *56*–443
Engstrom PF, *58*–217
Enot JK, *54*–273, *56*–421, *59*–327
Enriquez C, *55*–189
Ertel I, *56*–363,523, *59*–351
Escher GC, *58*–919
Espinoza JV, *59*–457
Etcubanas E, *58*–207,757
Evans AE, *52*–469, *53*–297, *58*–671, *59*–1015
Everson RB, *57*–353, *58*–353
Ezdinli E, *59*–333

F

Faber PJ, *59*–287
Fabro S, *52*–617
Fairly JL, *56*–739
Falkenhaug E-M, *55*–291
Falkson G, *52*–275, *54*–347, *55*–209,269, *56*–107,671,729, *58*–939
Falkson HC, *52*–275, *54*–347, *56*–107,671, *58*–939
Falletta JM, *56*–781, *58*–417,715
Farber S, *50*–629, *58*–5
Farmar RM, *54*–15
Fefer A, *58*–697,709, *59*–1131
Feldman EB, *56*–1
Feldman RG, *57*–73
Ferguson DJ, *58*–513
Fernbach DJ, *51*–381,412, *52*–287,293,441, *54*–283, *55*–67, *58*–417, *59*–395
Fewer D, *56*–421
Field EO, *55*–527
Field RB, *53*–199, *55*–159, *57*–383
Filippeschi S, *57*–115
Finegold SM, *54*–451
Fink A, *54*–451
Fink DJ, *54*–31
Finkel AJ, *50*–641
Finkel JM, *53*–159
Finklestein JZ, *53*–299, *54*–35, *56*–363,523, *57*–399,405, *59*–351,571,975,1015
Finn C, *59*–279
Firat D, *52*–743, *56*–259, *57*–423, *59*–1021
Fischer HW, *52*–119
Fischer JJ, *55*–193
Fischer RG, Jr, *59*–287
Fite A, *55*–79
Flatow FA, *53*–39
Fleischman RW, *58*–301, *59*–467
Fletcher WS, *50*–255,281
Fliegelman MJ, *59*–531
Foley GE, *50*–543,629
Foley HT, *51*–283, *55*–159
Foley JF, *54*–41
Foltz E, *58*–841
Fondy TP, *58*–317
Fonkalsrud EW, *57*–405
Fortuny IE, *59*–401
Fossati Bellani F, *58*–365
Fossieck BE, Jr, *59*–1171
Fowler EH, *57*–33

Foye LV, Jr, *54*–31
Fraimow W, *52*–99
Franchi G, *54*–79, *57*–115
Francis RS, *59*–1039
Franco P, *58*–325
Franzino A, *52*–425
Fraser TJ, *56*–709, *58*–149,157
Fredrickson TN, *52*–579,587
Freedman MH, *53*–299
Freeman AI, *54*–475
Frei E III, *50*–1, *55*–91,277,309,539, *56*–667, *57*–219, *58*–1,49,121, *59*–389
Freireich EJ, *50*–219, *52*–315, *53*–59, *54*–255, *56*–543, *57*–319, *58*–623, *59*–769
Frenkel EP, *51*–535
Friedman AE, *59*–233
Friedman OM, *50*–629, *51*–327,341,347,378
Froufe A, *59*–1025
Fruchtman B, *51*–41
Frytak S, *59*–405
Fugmann RA, *55*–239
Fujimoto S, *50*–313
Fujimoto T, *55*–285
Fukuoka F, *57*–85
Fukushima K, *59*–309
Funk DD, *58*–697,709
Furlow WL, *59*–203
Furner RL, *59*–717
Furue H, *56*–211

G

Gad-el-Mawla N, *57*–159, *59*–367
Gaeta JF, *59*–195
Gaetani M, *53*–33
Gailani SD, *50*–95, *54*–187, *55*–199
Gál F, *56*–593
Galbraith WM, *59*–1019,1061
Gallagher NI, *50*–649, *52*–627
Gallagher RE, *58*–579
Gallelli JF, *56*–387
Gallo RC, *58*–579
Gams RA, *58*–753
Gang M, *52*–399,715, *53*–229,265, *55*–9, *56*–327, *57*–291,299,383, *59*–689
Gangji D, *59*–1173
Gardere S, *56*–357
Garattini S, *54*–79, *57*–115
Garin AM, *58*–129
Gasparini M, *58*–365
Gass GH, *51*–431
Gastesi RA, *57*–225
Gaston MR, *58*–931, *59*–697
Gause GF, *58*–255
Gehan EA, *50*–219, *54*–225, *58*–623
Gehrke CW, *59*–721,1103
Geiser CF, *59*–385
Geller J, *51*–41
Gellhorn A, *51*–475
George P, *52*–509
George SL, *54*–225, *59*–395,437
Geran RI, *59*–729
Gerner RE, *57*–83,237
Gibbons RP, *59*–195
Gilchrist GS, *53*–299
Gillespie DH, *58*–579
Gitter S, *51*–271
Giuliani F, *57*–269
Glasofer ED, *59*–547
Gleason DF, *50*–125,129
Glidewell O, *55*–199, 269, *56*–729, *58*–233, *59*–557
Glucksberg H, *58*–697,709, *59*–1131
Glynn JP, *56*–683
Go LT, *57*–11
Godwin MC, *53*–385
Goepfert H, *52*–733
Goepp CE, *53*–79
Gold GL, *51*–277,283, *52*–425
Goldberg AI, *56*–683
Goldberg IH, *58*–81,479
Goldenberg IS, *50*–327, *55*–259
Goldin A, *50*–173,659, *52*–229,399,569,715, *53*–229,265,367, *54*–1,295, *55*–233,309,547, *56*–19,25,327,493,683, *57*–3,149, *58*–63,325,931, *59*–697,967
Goldman L, *52*–611
Gollin FF, *51*–189
Gomolka DM, *59*–127
Gonzalez-Palacios F, *59*–1025
Gordan GS, *54*–453
Gordon BS, *52*–563, *59*–891
Gordon HW, *53*–127
Gormley PE, *59*–1039
Gottlieb JA, *54*–365,369,461, *55*–277, *56*–103, *57*–219,437, *58*–265, *59*–621,665,769
Gouvalis P, *53*–255
Grage T, *52*–297,611, *56*–787
Gralla EJ, *59*–523,1071
Gray HB, Jr, *59*–611
Gray LG, *58*–157
Grayhack JT, *59*–139
Greenberg BG, *53*–1
Greenberg DM, *51*–455, *52*–687, *53*–195
Greenberg NH, *56*–483
Greenberg R, *58*–845
Greenier HJ, *50*–667
Greening RR, *52*–99
Greenspan EM, *56*–751
Gribble DH, *57*–235
Griffiths CT, *52*–413
Griswold DP, Jr, *52*–345, *53*–169, *54*–337
Grizzle JE, *53*–1
Grobmyer AJ III, *54*–243
Grogan RH, *52*–413
Grollman AP, *58*–491
Gross JF, *59*–819
Grossman J, *58*–125
Grunfeld C, *58*–491
Guarino AM, *54*–461, *57*–125
Gurland J, *50*–119
Gutterman JU, *57*–319,465
Guzzon A, *56*–343
Gyeskó A, *53*–115

H

Hadd HE, *59*–119
Haddy TB, *52*–287,293
Hadidian Z, *52*–579,587
Haggard ME, *51*–403, *52*–477, *54*–113
Hahn GM, *57*–473
Hahn RG, *51*–77, *53*–283, *54*–471, *55*–303, *56*–93,95,207,245,267,369,401,551,649, *57*–341,357,493, *58*–229,257,861,877,951, *59*–405,451,577,581,761
Halden A, *54*–453
Hall LM, *59*–629
Hall TC, *50*–259,685, *51*–35,197,231,277,335,503,517, *52*–413,425, *55*–595, *57*–41,353, *58*–353,429,441,909
Hamamura EK, *58*–451
Hammond CD, *50*–339, *53*–299, *56*–363,523
Hammond D, *59*–351,989,1097
Hammuda F, *57*–159
Hamza MIR, *57*–159
Han T, *59*–157
Handler AH, *50*–629
Haňka LJ, *54*–393, *55*–557, *57*–141, *58*–935, *59*–459
Hanley JA, *59*–333
Hansch C, *56*–433,443, *59*–327
Hansen HH, *55*–99,575,583, *56*–515, *58*–393, *59*–751,1027
Harada S, *59*–919
Haraphongse M, *59*–1139
Hardesty CT, *56*–611
Hardingham M, *56*–745
Harley JB, *51*–235
Harris J, *58*–167
Harris PA, *59*–819,985
Hart JS, *54*–255, *56*–543
Hart LG, *53*–211
Hart RG, *50*–295
Hartmann JR, *50*–339, *53*–297
Haskell CM, *53*–67, *56*–611
Hasselback R, *59*–537
Hattori T, *56*–211
Haurani F, *56*–535,729
Haut A, *50*–271, *58*–223, *59*–1163
Hayes DM, *51*–235, *58*–233
Hayes JW, *56*–781
Hazen JG, *50*–675, *51*–25
Hebborn P, *54*–23
Hedeman LP, *55*–101
Heidelberger C, *55*–29
Hellmann K, *55*–527
Helson C, *57*–191
Helson L, *56*–499, *57*–191
Henderson ES, *54*–47, *55*–309, *56*–755
Henderson JS, *58*–559
Henry MC, *59*–447
Hensleigh D, *59*–421
Herbert V, *57*–11
Herman EH, *54*–15, *58*–171,637
Hernandez KW, *51*–535, *53*–203
Herson J, *59*–3
Heshmat MY, *59*–3
Hessellund M, *59*–1027
Heston WDW, *59*–185
Hestorff R, *57*–481
Hewlett JS, *53*–59
Heyes J, *57*–263
Heyman IA, *58*–301
Heyn RM, *53*–297
Higashi H, *55*–29
Higby DJ, *57*–459
Higgins GR, *53*–299
Hilal HM, *55*–83
Hill AS, *59*–1131
Hill G, *56*–641,787
Hill JM, *59*–629,647
Hill LL, *56*–781
Hill NO, *59*–647
Himmelfarb P, *51*–451
Himori T, *57*–447
Hirano M, *56*–47,335
Hitannant S, *59*–1167
Hittle R, *59*–1015
Ho DHW, *55*–47,539
Hofer KG, *53*–273
Hoffman GS, *52*–715, *53*–199,265
Hoffman RV, Jr, *58*–745
Hogle HH, *53*–147
Holcomb TM, *51*–389, *52*–287,293,631
Holden EM, *57*–73
Holland JF, *50*–95, *51*–171,277, *52*–445,497, *55*–199,269,309, *56*–535,625,729, *57*–79,459,485, *58*–233, *59*–557
Holoye PY, *59*–377,433,563,1159
Holton CP, *52*–489, *54*–283, *58*–737
Homan ER, *51*–247
Hoogstraten B, *51*–235, *55*–199, *56*–535, *58*–943, *59*–1163
Hornes J, *52*–733
Horoszewicz JS, *59*–39,89
Horton J, *51*–197,277, *52*–425,597, *53*–291, *55*–253,281, *58*–677, *59*–333, 1127
Horváth IP, *51*–261, *53*–377
Hoshi A, *53*–165, *55*–229
Hoshino A, *56*–373
Hosley H, *53*–291
Houchens DP, *58*–931, *59*–697,967
Howard HTC, *59*–585
Howard JP, *50*–287, *51*–465, 535
Howard R, *59*–611
Howden MEH, *59*–585
Howe CD, *53*–135
Howe KE, *59*–629
Howsden FL, *54*–1
Hreschchyshyn MM, *52*–601
Hubbard SP, *55*–599, *57*–201,361
Huesser JN, *59*–1103
Huff J, *59*–1131
Hulbert MHE, *56*–745
Hum GJ, *57*–477, *59*–1177
Hummel RP, *52*–751
Humphrey EW, *50*–85, *53*–215, *56*–53,465
Humphrey GB, *57*–335,371, *58*–719, *59*–359,395
Humphrey RL, *58*–375
Humphreys SR, *51*–439, *52*–229, *54*–379
Hunt DE, *51*–213, *52*–553,707
Hurley JD, *54*–361
Hurwitz BS, *54*–263

Hussain S, *56*–357
Hutchison DJ, *50*–79, *52*–697, *55*–115,123, *56*–473,493, *57*–21, *59*–515,935
Hutchison GB, *59*–57
Hyde L, *58*–359
Hyltoft-Petersen P, *56*–229
Hyman CB, *52*–25, *53*–299
Hyman GA, *53*–39
Hyman R, *58*–431

I

Ibrahim AS, *57*–159
Ihde DC, *59*–1039
Ikawa Y, *57*–149
Ikekawa T, *57*–85
Ilievski T, *58*–301
Imai K, *56*–373
Institóris L, *51*–261, *53*–377, *56*–593
Iorio A, *59*–967
Irwin LE, *58*–723
Isaacs BL, *54*–119
Isassi AA, *51*–535, *52*–315
Izbicki R, *56*–615

J

Jackson AG, *59*–3
Jackson L, *52*–125
Jackson MA, *59*–3
Jackson RA, *59*–887
Jacobs EM, *51*–25, *56*–263, *57*–477
Jacobs SA, *59*–721
Jacobs SP, *54*–329
Jacobson HI, *58*–503
Jacquillat C, *56*–535
Jaffe N, *55*–189, *58*–275,661, *59*–389
James DH, Jr, *51*–411, *52*–489
Janicki BW, *52*–243
Jao-King C, *59*–1139
Jayaram HN, *58*–793, *59*–481
Jensen EV, *58*–513
Johns DG, *56*–249
Johnson CE, *51*–507
Johnson DE, *59*–17,195,433,563,1159
Johnson EC, *57*–59
Johnson IS, *52*–455
Johnson RE, *54*–103
Johnson RK, *57*–149, *58*–63, *59*–697
Johnson RO, *50*–119,671
Johnston CL, Jr, *59*–105
Joiner J, *59*–195
Jonas AM, *59*–523,1071
Jones B, *56*–729
Jones CTA, *56*–83
Jones GW, *59*–3
Jones R, Jr, *52*–641,655,661,667,675, *54*–53, *58*–689
Jones SE, *58*–733, *59*–887
Jönsson G, *59*–229
Jorgensen EO, *57*–241
Joseph WL, *58*–285
Journey LJ, *52*–509
Jungi WF, *59*–737
Jurkowitz L, *59*–333

K

Kabra P, *58*–787, *59*–327
Kaighn ME, *59*–59
Kaizer H, *55*–151
Kakizawa H, *56*–47,335
Kamei Y, *56*–373
Kane RC, *59*–1171
Kanzawa F, *53*–165, *55*–229
Kao MH, *52*–569
Kapadia A, *59*–843
Kapoor SK, *59*–3
Karakousis C, *59*–1035
Karker KL, *58*–317
Karon MR, *52*–473, *53*–299, *54*–35, *56*–363,523, *57*–399, *59*–989
Karrer K, *51*–439, *54*–379, *56*–35
Kashgarian M, *59*–1071
Katagiri K, *58*–451
Kataoka K, *56*–373
Kato T, *56*–373
Katz E, *58*–83
Katz JJ, *50*–641
Kaufman J, *59*–1007
Kaung DT, *52*–271, *55*–87, *58*–359
Kawashima K, *56*–47,335
Kelleher JK, *56*–557
Keller DL, *50*–89
Kelley RM, *52*–413
Kelley SA, *56*–31
Kellner B, *56*–593
Kelly F, *59*–47
Kende M, *56*–683
Kenderes R, *50*–89
Kenis Y, *52*–433, *56*–151, *59*–1173
Kennedy BJ, *51*–491, *59*–401
Kennedy J, *59*–3
Kensler CJ, *51*–415,423, *52*–251,393, *54*–329
Keyes JW, Jr, *55*–583
Khaliq A, *59*–769
Khan A, *59*–647
Khung CL, *51*–197, *52*–413
Kimball AP, *59*–611,661
King JJ, *59*–647
Kingra GS, *55*–281
Kinne DW, *56*–53
Kinney Y, *58*–931
Kirdani RY, *59*–175
Kiryabwire JWM, *55*–143
Kishi T, *59*–919
Kjellgren K, *55*–561
Kjobech C, *59*–1131
Klaassen DJ, *58*–667

Klein E, *59*–157
Klemperer M, *59*–1015
Kline I, *52*–399,715, *53*–199,229,265, *55*–9, *56*–327,483, *57*–291,299,383, *59*–689
Klipstein FA, *51*–475
Knapp KT, *53*–159
Knight E, *58*–677
Knudtzon S, *56*–221,229
Kociba RJ, *54*–325, *55*–1
Koehler PR, *52*–113,171
Kogler J, *56*–641
Kolarić K, *59*–1051
Komp DM, *57*–335,371, *58*–719, *59*–341,371,395
Koontz WW, Jr, *59*–105
Korbitz BC, *53*–243,249, *55*–183
Korman NP, *58*–135, *59*–888
Kostinas J, *59*–767
Kovach JS, *57*–341,357
Kovi J, *59*–3
Krakoff IH, *52*–635, *57*–191, *58*–207, *59*–1151
Krakower GW, *51*–225
Kralovánszky J, *53*–377
Kram-Idsenga LKJ, *56*–691
Krant MJ, *50*–107, *51*–277, *52*–425, *55*–253
Kreis W, *57*–349
Krementz ET, *50*–671, *51*–85
Kremer WB, *51*–19
Krivit W, *53*–53
Kudo T, *57*–447
Kuentzel SL, *54*–393, *58*–157, *59*–459
Kuffer FR, *53*–23
Kumagai K, *53*–165
Kung F, *52*–445, *56*–729
Kuo KC, *59*–721,1103
Kuperminc M, *56*–505, *57*–209
Kuretani K, *53*–165, *55*–229
Kurita S, *56*–373
Kurkjian S, *57*–473
Kurnick JE, *59*–1147
Kurokawa T, *56*–211
Kury G, *51*–363
Kuzma JW, *50*–113, *51*–25
Kyalwazi SK, *56*–249, *57*–65,325
Kyle RA, *59*–557

L

Lacave AJ, *59*–1025
Lahiri SR, *55*–595
Lakings DB, *59*–721,1103
Lambert A, *56*–175
Lamoureux KB, *58*–705
Land VJ, *57*–335, *58*–683,715, *59*–371
Lane DM, *54*–113,293, *55*–67, *58*–683, *59*–359
Lane M, *51*–341,359,377, *59*–425,1163
Lanzotti VJ, *59*–437
Larionov LF, *54*–71
Larsen V, *56*–71,769
Larson R, *50*–283
Laster WR, Jr, *50*–55, *51*–111, *53*–169,329,345, *56*–183,273, *59*–951
Laszlo J, *51*–19, *53*–131
Laucius JF, *56*–405,413
Lavie D, *51*–271
Lawton RL, *54*–237
Lazarus H, *50*–543
Leary WV, *53*–135
Lee BJ, *52*–205
Lee IP, *58*–171
Lee SH, *59*–661
Lee SL, *53*–203, *55*–199, *56*–535
Lefkowitz E, *51*–69,305
Lehane DE, *59*–1163
Leikin SL, *58*–671, *59*–1015
Lein EJ, *57*–251
Leiter J, *50*–349
Lelieveld P, *56*–691
Leme PR, *59*–811
Lemon HM, *54*–41
Lenaz L, *56*–153,431, *57*–269, *58*–769
Lenhard RE, Jr, *52*–305, *55*–509
Leone LA, *51*–81, *53*–203, *55*–199, *56*–535
Lerner HJ, *53*–385
Leroy JG, *50*–543
Lessner HE, *58*–407
Leventhal BG, *54*–47
Levi JA, *59*–1043
Levin B, *52*–189
Levin VA, *58*–627,787, *59*–327
Levin WC, *58*–223
Levine AS, *53*–53
Levy RN, *55*–199,269, *56*–535,729
Lewin N, *57*–803
Li LH, *56*–163, *58*–345
Lichinicer MR, *58*–129
Liciu F, *57*–29
Lieberman DZ, *59*–629
Lien EJ, *57*–251
Lien RC, *51*–85
Lin H, *59*–319,895
Lincoln TL, *59*–861
Lintrup J, *56*–229
Lippman AJ, *57*–191
Lippman MM, *56*–755, *57*–501, *58*–181
Liss RH, *58*–777, *59*–501
Littman ML, *50*–25
Liu A, *54*–89
Livingston RB, *57*–219,437
Lloyd HH, *53*–169, *54*–143,431, *56*–273,585, *59*–267
Lo KW, *57*–245
Loeb E, *59*–647
Loeb V, *53*–131
Lokey JL, *59*–767
Lokich JJ, *56*–653,761, *59*–389
Lomen PL, *59*–1123
Longeval E, *59*–1173
Lonsdale D, *52*–631, *54*–113, *55*–67
Loo RV, *51*–495
Loo TL, *50*–296, *55*–91, *59*–775,843
Louis J, *53*–71,121

Louis NB, *53*–71
Lucas AO, *59*–3
Lucas MB, *51*–229
Luce JK, *51*–535, *54*–119,131, *55*–91,277, *56*–103,667
Luciani L, *57*–429
Lukens J, *56*–729
Lusher J, *52*–287
Lutz RJ, *59*–795
Lynch J, *51*–277
Lynm D, *59*–233

M

Mackman S, *51*–167,483
MacLellan A, *59*–647
Maddock CL, *50*–629
Maezawa S, *57*–447
Magrath IT, *59*–1155
Mahmoud ME, *59*–367
Majima H, *56*–739
Malinin TI, *59*–91
Malkasian GD, Jr, *51*–507, *57*–241
Maltezeanu G, *54*–319
Manak RC, *59*–459
Manaster J, *59*–537
Mansson B, *55*–561
Mansy S, *59*–287
Mantel N, *50*–163,173, *53*–265, *54*–295, *56*–683
Manthei RW, *56*–405, *59*–547
Mantovani A, *58*–741
Marciniak TA, *59*–577,581,761
Marcus DM, *58*–491
Mardiney MR, Jr, *53*–3
Margulis L, *55*–531, *56*–557
Marsh JC, *55*–599,607
Marshall GL, *58*–723
Martin DG, *57*–141, *58*–935
Martin DS, *55*–239
Martin H, *51*–451
Maruyama K, *59*–17
Mashima Y, *56*–175
Mason JH, *52*–297, *55*–61
Mastrangelo MJ, *54*–109, *56*–413, *57*–185, *58*–217, *59*–1181
Matias PI, *51*–283, *55*–253
Matsumoto T, *58*–331, *59*–919
Mattioli F, *53*–13
Maura A, *56*–579, *58*–683
Maurer HM, *54*–65
Mauro F, *55*–527
Mayer CMH, *58*–737
Mayer K, *58*–207
Mayer SM, *59*–929
Mayo JG, *53*–169, *56*–183
Mazzone HM, *50*–543
McBride TJ, *58*–803
McBroom RE, *53*–71
McCormick JStC, *58*–889
McCredie KB, *56*–543, *57*–319,465
McInnis B, *59*–843
McMillan CW, *58*–715
Mealey J, Jr, *54*–9
Meares EM, Jr, *59*–165
Mehta BM, *59*–515,935
Meienhofer J, *58*–1,21
Mellett LB, *54*–431, *59*–717,1061
Mellette SJ, *56*–505
Mellinger GT, *50*–129, *51*–295
Mendelson D, *54*–365
Mengel CE, *51*–239
Merchant D, *59*–65
Merigan TC, *58*–571
Merker PC, *53*–99, *59*–729
Merriam P, *59*–467
Merrin C, *59*–97,157
Meshnik R, *59*–571,975
Meyer D, *58*–871
Meyers MB, *59*–515
Mhatre RM, *58*–171,637
Migliore RD, *58*–559
Mihich E, *54*–23
Miller D, *54*–41
Miller EE, *57*–245
Miller GW, *52*–243
Miller R, *53*–79
Miller SP, *50*–259, *51*–277,283
Milner AN, *51*–343
Mims CH, *58*–223
Mirand EA, *52*–557
Mitchell J, *53*–53
Mitchell MS, *55*–607
Mitchley BCV, *58*–645
Mittelman A, *56*–393, *59*–219,333,751,1007
Mitus JW, *59*–385
Miura M, *56*–47,325
Mizgerd JB, *55*–83
Mizuno NS, *50*–85, *53*–215, *56*–465
Modest EJ, *58*–35
Moertel CG, *51*–73,77, *53*–283, *54*–471, *55*–303, *56*–95,207,245,267,551,649, *57*–341,357,493, *58*–229,257,951, *59*–405,577,581,761,1103
Moffatt JG, *58*–451
Moldovanu G, *53*–223
Moncure CW, *59*–105
Monfardini S, *56*–343
Montgomery JA, *54*–431
Monto RW, *53*–59,121, *54*–293
Moon JH, *51*–235, *52*–445, *54*–245, *55*–269
Moore AL, *54*–89
Moore GE, *52*–641,655,661,667,675, *57*–83,237
Moorhead EL II, *52*–593
Morasca L, *57*–115
Morgan S, *57*–371
Morita A, *56*–47,335
Morrison AN, *55*–199
Morrison PF, *59*–861
Morrison RK, *54*–217
Morin JE, *50*–327
Morris HP, *57*–245
Mosbach EH, *50*–25
Mosher MD, *58*–759
Mostofi FK, *59*–111

Movassaghi N, *59*–989,1097
Moxley TE, *56*–163, *58*–345, *59*–459
Mrazek RG, *52*–751, *54*–361
Muggia FM, *51*–475, *53*–39, *55*–99,575, *56*–515,573, *58*–421,919, *59*–751
Müller W, *58*–97
Mulligan LT, *53*–159
Mullins GM, *59*–411
Munchausen LL, *59*–643
Munson AE, *51*–253
Murakami M, *56*–373
Murphy GP, *56*–393, *59*–1,97,157,175,195,219
Murphy ML, *50*–287,399, *51*–363, *53*–23, *56*–499
Mussey E, *51*–507
Musumeci R, *57*–429, *58*–365
Myers RP, *59*–203

N

Nadler SH, *52*–425,641,655,661,667,675
Nagamoto A, *55*–151
Nagatsu M, *56*–175
Nahas A, *58*–909
Nathanson L, *50*–259, *51*–35,503, *56*–659
Nathanson N, *54*–211
Nealon T, *58*–653,663
Necco A, *57*–269, *58*–769
Neely M, *59*–327
Neil GL, *54*–393, *56*–163,709, *57*–141, *58*–157,345,935, *59*–459,481,501,1123
Neiman PE, *58*–697,709, *59*–1131
Nelson JF, *51*–59
Németh L, *56*–593
Nemoto T, *58*–677
Nesbit ME, *53*–53,297
Newman AD, *59*–629
Newman H, *51*–41
Newman JW, *55*–309
Newman SJ, *58*–901
Newton WA, Jr, *52*–257, *59*–17
Nicol NT, *56*–89
Nicolin A, *57*–3, *58*–325
Nieglos MA, *54*–217
Nilprabhassorn P, *59*–1167
Nilsson T, *59*–229
Nishimura M, *56*–373
Nishiwaki H, *56*–47,335
Nissen NI, *56*–71,221,229,769, *59*–1027
Nissen-Meyer R, *55*–561
Nitschke R, *59*–371
Nkposong EO, *59*–3
Nkrumah FK, *59*–1155
Nora AH, *52*–631
Nora PF, *50*–573
Norman RL, *58*–296, *59*–257
Norrell H, Jr, *51*–1
Noyes WF, *59*–67
Nyhan WL, *52*–445

O

Oberfield RA, *56*–535
O'Bryan RM, *50*–335, *54*–249, *57*–225,465
Ochoa M, Jr, *59*–1151
O'Connell MJ, *58*–401, *59*–443
Odujinrin OO, *59*–1091
Ogawa M, *56*–373
Ohira S, *57*–447
Ohno R, *56*–47,335
Ohnuma T, *55*–269, *56*–625
Ohtsuki Y, *59*–17
Okada Y, *58*–331
Oldham RK, *56*–635
Olin EJ, *58*–345
Olisa E, *59*–3
Oliverio VT, *53*–211, *54*–461, *55*–215
Olshin S, *52*–743, *56*–259, *57*–423
Olson BH, *55*–101, *56*–725
Olson KB, *51*–197,277, *52*–597, *53*–291, *55*–281
Olweny CLM, *59*–721
Ootsu K, *58*–331, *59*–919
Origenes ML, Jr, *50*–339
Ortega JA, *56*–363
Osbaldiston GW, *59*–523,1071
Osman A, *57*–159, *59*–367
Ostrovskaya LA, *58*–135, *59*–888
Ostrowski W, *59*–97
Ota K, *56*–373
Otis PT, *58*–841
Ott F, *55*–59
Ottoman RE, *52*–733
Owens AH, Jr, *51*–277, *52*–305, *58*–383
Owor R, *57*–65
Oyama A, *56*–373

P

Pajak TF, *57*–419
Paladine WJ, Jr, *53*–291
Pályi I, *53*–115, *56*–593, *59*–493
Pang EM, *58*–671
Papac RJ, *51*–69,305, *55*–193
Papaioannou AN, *50*–323
Papakyriakides L, *53*–255
Papas TS, *57*–305, *58*–821
Papavasiliou C, *53*–255
Parise F, *55*–167
Parodi S, *53*–13
Paterson ARP, *51*–101
Patno ME, *52*–271, *54*–451, *55*–83,87, *56*–739
Patterson RB, *56*–729
Paul BD, *59*–233
Paul H, *56*–1
Paulson A, *58*–709
Paulson DF, *59*–51
Peale A, *59*–985
Pearson JW, *57*–305
Pedersen H, *56*–769, *59*–1027

Peresie HJ, *59*–287
Perkins IV, *59*–1155
Perlia CP, *58*–871, *59*–995
Perlin E, *59*–767
Perlman D, *51*–225, *58*–93
Perloff M, *58*–421,919
Perry S, *58*–117
Petering HG, *50*–557
Peters RL, *50*–675
Pethes G, *51*–261
Petty W, *57*–413
Phelen R, *58*–301
Philips FS, *50*–9, *55*–35
Phillips LK, *58*–737
Phillips RW, *52*–417, *54*–181, *55*–567
Piel IJ, *58*–871, *59*–995
Pierce MI, *52*–321, *58*–671
Pinch P, *57*–201
Pinkel D, *52*–489, *53*–203
Pinkerton D, *59*–341
Piro AJ, *55*–595
Pisciotta AV, *53*–121
Pittillo RF, *51*–213,229, *52*–553,707, *54*–137, *55*–47,221, *57*–275, *58*–311
Piver MS, *59*–1157
Place CH, *58*–749
Plager J, *56*–393
Plapinger RE, *59*–233
Platt DS, *56*–83
Pleuss HJ, *56*–729
Pomeroy TC, *56*–635
Pontes JE, *59*–147
Popescu N, *57*–29
Popović S, *59*–1051
Porcile G, *59*–890
Prager MD, *56*–339
Pratt CB, *52*–489, *59*–743
Pratt KL, *53*–291
Prentice R, *56*–739
Preston FW, *50*–573
Pretlow TG II, *59*–143
Price FW, *52*–557
Price NA, *58*–189
Price RA, *57*–165
Primack A, *57*–65,325, *58*–901
Prohaska JV, *51*–85
Propst S, *56*–557
Prout GR, *59*–195
Prystasz M, *58*–451
Pugh RP, *57*–481, *58*–947, *59*–1031
Pullen DJ, *59*–359

R

Rabinov D, *51*–49
Ragab AH, *59*–359
Rahn RO, *59*–643
Rainen L, *59*–611
Rakieten N, *52*–563, *59*–891
Rall DP, *50*–219,283, *51*–247
Ramirez G, *51*–483, *52*–611, *53*–243,249, *55*–183,205,265, *56*–787, *57*–59
Rao KV, *58*–803
Rapp E, *58*–667
Rapp F, *59*–33
Ravry M, *57*–493
Ray GR, *57*–473, *59*–165
Razek AA, *59*–395
Redding RA, *58*–301
Reed A, *59*–989,1097
Reed LJ, *51*–475, *58*–919
Reed ML, *50*–565, *51*–497, *56*–615
Rege VB, *51*–81, *58*–383
Regelson W, *51*–171,277, *56*–505, *57*–209
Reich C, *59*–51
Reich E, *58*–79
Reich SD, *59*–677
Reid JW, *59*–767
Reitemeier RJ, *51*–73,77, *53*–283, *54*–471, *55*–303, *56*–95,207,245,267,551,649, *57*–357,493, *58*–229,257,951, *59*–405,577,581,761
Reiter W, *59*–765
Reuvers AP, *58*–559
Reyes ES, *57*–225
Ricci JA, *54*–243
Richards F II, *57*–419
Richards JF, *52*–463
Ridgway H, *59*–629
Rimm AA, *50*–141, *52*–641,655,661,667,675
Ritts RE, Jr, *58*–913
Riva A, *59*–1161
Rivas A, *59*–1025
Rivera G, *59*–743
Roberts D, *57*–165
Roberts J, *58*–829
Roberts T, *51*–41
Robins RK, *53*–147
Robinson WA, *59*–1147
Rochlin DB, *50*–671, *52*–297,733, *55*–61,265
Rodriguez A, *59*–457
Rodriguez L, *59*–1159
Rodriguez V, *54*–255, *57*–319
Roesler AR, *59*–447
Roga V, *55*–101
Rogers WI, *52*–337
Rohn RJ, *53*–121
Rohner TJ, *59*–33
Rose NR, *59*–147
Rose S, *51*–49,59
Rosenbaum C, *58*–677
Rosenberg B, *54*–325, *58*–619, *59*–287,589
Rosenberg PJ, *59*–377
Rosenberg SA, *52*–213
Rosenblum ML, *55*–99
Rosner D, *58*–677
Rosner F, *52*–445, *55*–167,199,269, *56*–729
Ross CA, *57*–79
Rossi A, *59*–1161
Rosso R, *54*–79, *59*–890
Roth A, *59*–1051
Rothberg H, *58*–749
Rothberg L, *56*–339

Rothenberg L, *54*–303
Rubin H, *55*–167
Rubin RC, *50*–283
Rudders RA, *59*–421
Rusconi A, *52*–331
Rush BF, Jr, *50*–331
Russell AF, *58*–451
Rutenberg A, *51*–35
Rutner H, *58*–803
Ryan JA, *58*–793, *59*–481
Ryssel HJ, *59*–429

S

Saarinen P, *57*–399
Sadee W, *59*–279
Sadoff L, *54*–457, *56*–61,559, *58*–125
Sáenz R, *50*–265
Saito R, *57*–489
Saito T, *57*–447
Sakamoto A, *58*–413
Sako K, *56*–625
Sakurai Y, *54*–311, *56*–9, *57*–159, *59*–367
Salem P, *59*–1117
Salmon SE, *50*–685, *51*–179, *58*–733, *59*–345
Salzman JR, *59*–165
Samson MK, *59*–1123
Samuels LD, *52*–257
Samuels ML, *52*–315, *53*–135, *59*–377,433,437,563,1159
Sandberg AA, *59*–175
Sandberg JS, *53*–367, *54*–1, *55*–233, 309
San Diego EL, *52*–593, *54*–249
Sandler SG, *52*–519
Sanford EJ, *59*–33
Sano T, *57*–85
Saroff J, *59*–195
Sato G, *59*–47
Sato K, *58*–451
Satoh H, *56*–9
Savel H, *53*–153
Savlov ED, *58*–909
Sawarnkatata P, *59*–1052
Sawicki WL, *59*–523
Sayers MP, *52*–257
Sbar S, *52*–271, *55*–87
Scarpinato BM, *53*–33, *56*–153
Schabel FM, Jr, *50*–55,247,299, *51*–7,111,125, *52*–345, *53*–169,329,345, *54*–137,337,431, *56*–183,273,493, *59*–261,951
Schaeppi U, *58*–301, *59*–467
Schafer MP, *58*–821
Schantz A, *58*–401
Schechter JP, *59*–887
Schein PS, *52*–563, *54*–15, *57*–361
Schell HW, *50*–683
Schepartz S, *50*–349
Scher J, *54*–35
Schick M, *50*–319
Schick S, *57*–489
Schilling A, *50*–685, *51*–179,517
Schimpff SC, *59*–1055
Schmeer MR, *50*–655
Schmid FA, *55*–115,123, *56*–473, *57*–21, *58*–829
Schmidt JD, *59*–195
Schmidt LH, *50*–219, *56*–493
Schneiderman MA, *50*–107, *54*–294
Schneyer CA, *59*–1019
Schofield B, *50*–47
Scholler J, *51*–205
Schreiber W, *55*–591
Schroeder JM, *51*–525, *54*–237
Schutt AJ, *54*–471, *55*–303, *56*–95,207,267,551,649, *57*–341,357,493, *58*–229,257,951, *59*–405,577,581,761
Schwartz HS, *58*–55
Schwartzbach E, *56*–315
Scott WW, *59*–195
Sears ME, *50*–271
Seay DG, *56*–89
Sedransk N, *56*–641
Segaloff A, *50*–671, *51*–253, *55*–259
Segarra JM, *57*–73
Selawry OS, *52*–497, *55*–575,583, *56*–515, *58*–393,901, *59*–751,1001
Seligman AM, *59*–233
Seligman BR, *59*–557
Sellei C, *53*–377
Sellers SM, *50*–299
Seman G, *59*–17
Semar JB, *51*–225
Semonský M, *57*–311
Sengupta SK, *58*–35
Senn HJ, *59*–737
Senyszyn JJ, *54*–103
Serio G, *59*–611
Serpick AA, *50*–173, *53*–3,49, *54*–199,365,369, *55*–199
Severo N, *50*–339
Shackney SE, *54*–399
Shadduck RK, *50*–685, *51*–35,179,197,517
Shah KV, *59*–51
Shannon WA, Jr, *59*–233
Shapiro WR, *56*–457
Sharief Y, *59*–51
Sharp HL, *53*–53
Shedd DP, *56*–625
Shimoyama M, *55*–123
Shiratori O, *58*–451
Shnider BI, *51*–283, *52*–425, *55*–253, *58*–689
Shoemaker JP, *58*–745
Shohat B, *51*–271
Shore NA, *53*–299
Shorin VA, *58*–255
Showalter D, *58*–845
Shteir O, *58*–749
Shukla SK, *59*–219
Siddiqui S, *56*–259, *57*–423
Sidwell RW, *50*–299
Sieber SM, *58*–617, *59*–599,915
Sieper WJ, *59*–1181
Silva AR, *52*–733
Silva R, *51*–41
Silver RT, *55*–269, *56*–535, *58*–233, *59*–557
Simon R, *59*–1155

Simpson AI, *51*–101
Simpson CL, *54*–23
Simpson-Herren L, *52*–345, *53*–169,329, *54*–143,337, *56*–273
Sirica A, *56*–327
Sitarz AL, *59*–989,1097
Skarin AT, *56*–653,761
Skeel RT, *54*–47
Skinner WA, *51*–205
Skipper HE, *50*–55,219, *51*–111,125, *52*–345, *53*–169,329,345, *54*–137,431, *56*–273,493
Skovsgaard T, *59*–301
Slack NH, *50*–151, *52*–641,655,661,667,675, *54*–53
Sleight SD, *54*–325, *55*–1
Sloan WR, *59*–185
Smart CR, *52*–733, *53*–147
Smith ER, *52*–579, 587
Smith F, *59*–1117
Smith MJV, *59*–105
Smith N, *56*–443
Smith P, *59*–209
Smith RG, *58*–579
Smith S, *58*–513
Smith TL, *59*–377
Sobell HM, *58*–101
Sodergren JE, *55*–35
Solidoro A, *50*–265
Solomon J, *57*–477
Somfai S, *56*–593
Sonntag RW, *56*–197, *59*–429
Soranzo C, *57*–269
Southwest Cancer Chemotherapy Study Group, Adult Division, *50*–271
Spahn G, *57*–305
Speer RJ, *59*–629
Spiegelman S, *58*–595
Spigel SC, *58*–213
Sponzo RW, *57*–361, *59*–1127
Spreafico F, *58*–741
Springer K, *53*–105
Spurr CL, *57*–419
Stadnicki SW, *58*–301, *59*–467
Staley CJ, *52*–405
Stambaugh JE, *56*–405,413, *59*–547
Stark DB, *50*–281
Starkweather DK, *57*–125
Starling KA, *54*–113,293, *56*–781, *57*–335, *58*–417,683
Stashick E, *54*–125
Steeves RA, *52*–557
Steinfeld JL, *50*–675, *51*–25
Stephens RL, *58*–943, *59*–1163
Sternberg SS, *50*–9, *55*–32
Sternberger NJ, *59*–233
Steuber CP, *56*–781, *58*–417
Stewart DP, *59*–629
Stewart T, *58*–167
Stjernholm RL, *56*–527
Stock CC, *54*–299, *57*–21
Stolfi RL, *55*–239
Stolinsky DC, *51*–25, *56*–263, *57*–477,481,497, *58*–249,947, *59*–1031
Storb R, *58*–697,709
Stott PB, *52*–593
Straus MJ, *56*–19,25
Strawitz JG, *52*–611, *58*–217
Street EW, *58*–621
Strøyer I, *59*–1027
Stryckmans P, *56*–151, *59*–1173
Stuckey WJ, Jr, *52*–293, *59*–395
Sugár J, *53*–115, *56*–593
Sugawara N, *57*–447
Sugiura K, *53*–189
Sullivan J, *52*–597, *53*–291
Sullivan MP, *51*–343,393, *52*–293,481,631, *54*–113, *55*–151, *57*–319,335
Sutow WW, *51*–407, *52*–287,441,485, *54*–283,293, *55*–67,151,285, *58*–683, *59*–341
Suzuki S, *56*–9
Swiniarski JK, *51*–415,423, *52*–251,393, *59*–939
Szentirmay Z, *56*–593
Szybalski W, *58*–539

T

Taft PD, *51*–231
Taguchi T, *50*–25
Takagaki Y, *56*–9
Takahashi H, *57*–447
Takahashi M, *52*–81,157
Takita H, *58*–371
Talley RW, *50*–335, *51*–171, *52*–593, *53*–119,249, *56*–667, *57*–225,231,465, *59*–425,1117
Tan C, *50*–95, *56*–499, *58*–207
Tarnowski GS, *57*–21
Tarsy D, *57*–73
Tashima CK, *58*–618, *59*–441
Taub RJ, *58*–759
Taylor G, *52*–453
Taylor SG III, *58*–393, *59*–333
Taylor SG IV, *58*–677, *59*–1127
Tegeler W, *50*–543
Tejada F, *59*–243,751,1001
Tekuzman G, *59*–1021
Tel E, *58*–627
ten Pas A, *56*–535
Terselic RA, *54*–303
Thayer PS, *51*–451
Theologides A, *59*–401
Thetford B, *55*–539
Thomas ED, *58*–697,709, *59*–1131
Thompson SA, *50*–55
Thomsen K, *56*–769
Thomson JWW, *58*–889
Threefoot SA, *52*–1,107
Thurman WG, *51*–399, *52*–631, *54*–119,283,293
Timmens EK, *54*–217
Ting RC, *58*–579
Tisman G, *57*–11
Tittle K, *59*–571,975
Tobin W, *52*–519
Todd IDH, *56*–83
Tolen S, *55*–43
Tong GL, *57*–251

Tormey DC, *57*–51,413, *59*–1103
Toya T, *57*–325
Toyoshima S, *59*–309
Trader MW, *50*–55, *53*–329,345, *56*–273
Traggis D, *55*–189, *58*–661
Tranum BL, *59*–1163
Treat CL, *56*–729
Treble DH, *53*–291
Troetel WM, *56*–405, *59*–547
Trouet A, *59*–260
Tsou KC, *57*–245
Tsukagoshi S, *52*–569, *54*–311, *56*–9
Tucker WG, *52*–593, *59*–425
Turnell RW, *58*–353
Turner AF, *52*–59
Tyrer DD, *52*–399,715, *53*–229,265

U

Uchida N, *58*–451
Uetani T, *56*–47,335
Uijiie S, *57*–447
Ultmann JE, *53*–39
Umsawasdi T, *59*–1052,1167
Urtesun RC, *59*–1139
Utz DC, *59*–203

V

Vadlamudi S, *55*–547, *57*–3
Vaitkevicius VK, *50*–565, *51*–497, *56*–615,667, *57*–231, *59*–1117
Valaitis J, *52*–405
Valdes OS, *54*–65
Valeriote F, *55*–43, *59*–895
VanCamp L, *59*–287
van der Merwe AM, *56*–107,671, *58*–939
van Dyk JJ, *52*–275, *56*–107, *58*–939
van Eden EB, *54*–347, *56*–107, *58*–939
van Elk J, *52*–405
Vanichayangkul P, *56*–499
van Putten LM, *56*–691
Varkarakis MJ, *59*–97,175
Vaughn CB, *51*–497, *56*–615
Vecchi A, *58*–741
Velez-Garcia E, *58*–895
Venditti JM, *50*–659, *51*–377, *52*–399,715, *53*–229,265, *54*–329, *55*–9, *56*–327,483,493, *57*–291,299, *59*–689
Vergara JR, *59*–51
Verheyden JPH, *58*–451
Vermel EM, *58*–135
Vermund H, *51*–189, *58*–841
Verzosa M, *55*–79
Viamonte M, *52*–65,147
Vidal PM, *50*–9, *55*–35
Vietti TJ, *51*–535, *52*–287,441,631, *55*–67,151,285, *58*–719, *59*–341
Viranuvatti V, *59*–1167
Vogel CL, *55*–143,159, *56*–249, *57*–65,325
Vogel V, *58*–401
Vogler WR, *58*–407,895
Volk H, *50*–323
Vuthibhagdee P, *55*–285

W

Waalkes TP, *59*–721,1103
Wajsman Z, *59*–157
Wakui A, *57*–447
Walcroft MJ, *59*–319
Walker DG, *52*–543
Walker DJ, *58*–189
Walker MD, *54*–263, *55*–99
Wallace HJ, Jr, *57*–459,485, *59*–557
Wallace S, *52*–31,99,125
Wallach D, *58*–157
Walsh WS, *52*–271
Walsh-Waring GP, *56*–745
Walter RM, *54*–453
Wampler GL, *56*–505, *57*–209
Wang MC, *51*–101
Wanume AK, *57*–325
Waravdekar VS, *53*–199
Ward SB, *57*–393
Ware DE, *59*–1147
Warnecke MA, *52*–627
Wasserkrug HL, *59*–233
Watanabe A, *55*–285
Watkins WL, *52*–293, *54*–283
Webb MJ, *57*–241
Weeth JB, *51*–525
Weil M, *55*–199
Weiner J, *59*–571,975,989,1097
Weiner MJ, *56*–751
Weiss AJ, *52*–611, *53*–79, *54*–109, *55*–61,265,299,525, *56*–405,413,641, *58*–217,653, *59*–547
Weiss HD, *58*–927
Weiss L, *52*–21
Welvaart K, *59*–219
West C, *58*–189
Wheeler DMS, *59*–258
White M, *59*–1147
Whitecar JP, Jr, *56*–543
Whittington RM, *54*–195,451, *56*–739
Wiernik PH, *53*–49, *58*–261,927, *59*–443,1043
Wiig KM, *59*–847
Wilbur JR, *55*–151,285, *58*–281,757
Wilcox WS, *50*–541, *51*–125, *52*–345
Wilkoff LJ, *51*–7, *52*–725, *54*–431, *56*–585
Will J, *53*–71
Williams AO, *59*–3
Williams KO, *53*–299
Williams TE, *58*–715
Wilmanns H, *51*–397
Wilson CB, *51*–1,201, *54*–273, *56*–421, *58*–627, *59*–327
Wilson HE, *53*–71,121, *56*–667
Wilson KS, *57*–243
Wilson W, *58*–653

Wilson WL, *50*–671, *51*–85,471, *52*–297,301,751, *54*–361, *55*–299,525, *56*–641,787
Wilson WW, *53*–127
Wirtanen GW, *52*–263
Wittes RE, *59*–1151
Wittliff JL, *57*–353, *58*–353
Wodinsky I, *51*–415,423, *52*–251,393, *54*–329, *56*–31,315,493, *59*–729,939
Wohl H, *56*–729
Wolf J, *58*–359
Wolfe VI, *58*–871
Wolff JA, *52*–321
Wolff SM, *57*–393
Wollner N, *56*–499
Wolman IJ, *52*–497
Woo KB, *59*–847
Wood DA, *51*–25
Wood HB, Jr, *56*–443, *57*–305
Woodbury EC, *58*–803
Woodman RJ, *55*–9, *56*–327, *57*–291,299,383, *59*–689
Woods WA, *57*–305, *59*–531
Woolley C, *55*–47,221, *57*–275, *58*–311
Wu AM, *58*–579

Y

Yamada K, *56*–47,335
Yamaguchi K, *58*–451
Yamanaka H, *59*–175
Yankee RA, *54*–47
Yarbro JW, *57*–185, *58*–217
Yates JW, *56*–237, *57*–485
Yesair DW, *56*–315
Yokoyama M, *57*–447
Yoshioka Y, *57*–85
Young RC, *56*–387, *57*–361
Yount WJ, *50*–259,685, *51*–517

Z

Zager R, *56*–755
Zaharko DS, *54*–95, *59*–795
Zâmečník J, *57*–311
Zbinden G, *59*–707
Zeigel RF, *59*–39
Zelen M, *58*–359
Ziegenfuss J, *59*–547
Ziegler JL, *55*–143, *59*–1155
Zimmer MJ, *52*–627
Zubrod CG, *50*–349, *57*–373
Zumwalt RW, *59*–721,1103

Author Index

A

Abbott BJ, *4(3)*:1, *4(4)*:53, *5(1)*:15
Artis EW, *2(1)*:65, *3(1)*:1

B

Blanz EJ, Jr, *2(1)*:177,199
Block JB, *4(4)*:27
Bono VH, Jr, *4(1)*:131, *5(1)*:205
Brockman RW, *4(1)*:115
Brown GF, *2(1)*:141, *3(1)*:231
Byfield JE, *5(1)*:205

C

Caldwell IC, *2(1)*:237, *3(1)*:71
Cappuccino JG, *1(2)*:403
Carter SK, *4(1)*:3, *5(1)*:235
Chan MC, *3(1)*:71
Chang CF, *4(3)*:1
Cheeks JB, *4(1)*:53
Christoffersen RE, *4(4)*:47
Chu MYW, *2(1)*:57
Congleton GF, *4(4)*:53
Connors TA, *5(1)*:133
Corbett TH, *5(1)*:169
Cosby LA, *4(4)*:23
Craig PN, *4(4)*:39

D

Davies AJS, *5(1)*:133
Detre SI, *5(1)*:133
Dominick CA, *4(1)*:99
Downs WG, *2(1)*:57
Driscoll JS, *3(1)*:121, *4(2)*:1, *4(4)*:1,3,33
Dudeck LE, *4(4)*:53
Dykes DJ, *4(1)*:99

E

Engle RR, *1(1)*:1, *3(1)*:137
Evans RD, *5(1)*:243

F

Fischer GA, *2(1)*:57
Folkers K, *4(4)*:19
French FA, *2(1)*:177,199
Fugmann RA, *4(1)*:13,25, *5(1)*:89

G

Gadd REA, *1(2)*:363
Gang M, *2(1)*:65, *3(1)*:1
Gargus JL, *4(4)*:53
Geran RI, *4(4)*:53, *5(1)*:15
Goldin A, *1(1)*:1, *1(2)*:273, *2(1)*:65,135, *3(1)*:1,111,121,137, *4(2)*:1, *4(3)*:97, *5(1)*:21,111
González R, *2(1)*:141
Gordon HL, *2(1)*:27
Greenberg NH, *5(1)*:15
Griswold DP, Jr, *3(1)*:315, *4(1)*:99, *5(1)*:169,187

H

Hagemann RF, *5(1)*:205
Hansch C, *4(4)*:51
Hartwell JL, *4(3)*:1,97
Hayworth PE, *4(1)*:13,25, *5(1)*:89
Hazard GF, Jr, *4(2)*:1
Henderson JF, *1(2)*:363,375, *2(1)*:237, *3(1)*:71,87,95
Henry DW, *4(4)*:5
Himmelfarb P, *2(1)*:1
Hsu HM, *4(3)*:1

J

Johnson RK, *5(1)*:21,111

K

Kaufman JJ, *4(4)*:49
Kelley CA, *4(1)*:99
Kensler CJ, *4(1)*:73
King ML, *4(3)*:1
Kline I, *2(1)*:65, *3(1)*:1, *4(1)*:33
Kojima R, *3(1)*:111,121
Kowalski BR, *4(4)*:43

L

Laster WR, Jr, *4(1)*:53, *5(1)*:151
Lau KF, *3(1)*:71,87,95
Lesher SH, *5(1)*:205
Li CP, *4(3)*:97
Lichter W, *4(1)*:109
Lin AJ, *4(4)*:23
Lloyd HH, *4(1)*:157, *5(1)*:243
Lopez DM, *4(1)*:109
Love JW, *5(1)*:243

M

Macdonald MM, *2(1)*:27, *5(1)*:15
Mancher RR, *4(1)*:167
Mantel N, *3(1)*:111,121, *4(1)*:147
Marlow M, *5(1)*:145
Martin DS, *4(1)*:13,25, *5(1)*:89
Martin YC, *4(4)*:35
Masilungan VA, *2(1)*:135
Mayo JG, *3(1)*:325
Mead JAR, *1(2)*:273
Medina D, *5(1)*:127
Merker PC, *5(1)*:225
Miller I, *4(1)*:151, *5(1)*:5
Miller W, *4(4)*:27
Miller WT, Jr, *5(1)*:253

O

Ovejera AA, *5(1)*:111

P

Paterson ARP, *3(1)*:71
Paul B, *3(1)*:71
Peckham J, *5(1)*:169
Purcell WP, *4(4)*:41

Q

Quinn FR, *4(4)*:31

R

Rao KV, *4(4)*:11
Roberts BJ, *4(1)*:99, *5(1)*:169

S

Sandberg JS, *3(1)*:137
Sartorelli AC, *4(4)*:23
Schabel FM, Jr, *3(1)*:309, *4(1)*:53, *5(1)*:169
Schmid FA, *1(2)*:403, *2(1)*:141, *3(1)*:231
Schmid MM, *3(1)*:231
Serpick AA, *4(4)*:27
Shefner AM, *5(1)*:145
Sigel MM, *4(1)*:109
Simpson-Herren L, *5(1)*:83
Skipper HE, *4(1)*:53,137
Stim TB, *2(1)*:57
Stock CC, *1(2)*:403
Stolfi RL, *4(1)*:13,25, *5(1)*:89
Stone S, *5(1)*:5
Sugiura K, *1(2)*:383, *2(1)*:141, *3(1)*:231
Swiniarski JK, *4(1)*:73, *5(1)*:215,225

T

Tarnowski GS, *1(2)*:403
Thayer PS, *2(1)*:1,27
Topliss JG, *4(4)*:37
Trader MW, *4(1)*:53
Tyrer DD, *2(1)*:65, *3(1)*:1

U

Unger SH, *4(4)*:45

V

Vadlamudi S, *2(1)*:135
Valeriote FA, *5(1)*:205
Venditti JM, *2(1)*:65, *3(1)*:1,137, *4(1)*:1,73, *5(1)*:1,21,215,225
Vietti T, *5(1)*:205

W

Wang CT, *4(3)*:1
Wang SJ, *4(3)*:1
Wasserman TH, *5(1)*:235
Watts GL, *2(1)*:1
Wiernik PH, *4(4)*:27
Wodinsky I, *4(1)*:73, *5(1)*:215,225
Wood HB, Jr, *1(1)*:1, *1(2)*:273, *3(1)*:137, *4(2)*:1
Woodman RJ, *4(1)*:45

Author Index

A

Abbott BJ, *3(2)*–1
Ahmann DL, *3(1)*–29; *6(2)*–335,339
Alberto P, *4(2)*–199
Alth G, *4(2)*–271,275
Anderson RM, *4(3)*–51
Arcamone F, *6(2)*–123
Atassi G, *6(2)*–131

B

Bachur NR, *4(3)*–47; *6(2)*–153
Bajetta E, *4(2)*–231; *6(2)*–231
Baker JR, *4(1)*–31
Baker LH, *6(2)*–271
Balcerzak S, *6(2)*–271
Barranco SC, *6(2)*–147
Barry LM, *4(2)*–137
Bender RA, *6(1)*–73
Benjamin RS, *6(2)*–183,191,195
Beretta G, *6(2)*–231
Bisel HF, *6(2)*–335,339
Blum RH, *6(2)*–247
Blumenschein GR, *6(2)*–271
Bodey GP, *4(2)*–227; *6(2)*–271
Bogden AE, *5(1)*–43
Bonadonna G, *4(2)*–231; *6(2)*–231,381
Bottomley R, *6(2)*–271
Bozzetti F, *4(2)*–101
Brambilla C, *6(2)*–231,381
Brown DE, *4(1)*–41
Brugarolas A, *4(2)*–257,293
Brunner KW, *4(2)*–125
Bucalossi P, *4(2)*–101
Burgess MA, *6(2)*–203,271,361
Bychkov MB, *4(2)*–251

C

Capizzi RL, *6(1)*–37
Carbone PP, *3(1)*–73
Carr DT, *4(2)*–17,303
Carter SK, *1(1)*–63,81,99,115,153,165,179,207; *2(1)*–81; *3(1)*–33; *4(2)*–109,265; *4(3)*–35; *6(2)*–389,399
Castles TR, *4(1)*–51
Chabner BA, *6(1)*–1,19
Chandra P, *6(2)*–115
Coleman GL, *5(1)*–1,79
Coltman CA, Jr, *6(2)*–271,375
Comis RL, *6(2)*–399
Cookson KM, *5(1)*–15
Cooney DA, *4(1)*–1,31,41,85,103,121; *5(1)*–25,43
Cortes EP, *6(2)*–215,305
Cradock JC, *4(3)*–7

D

Dana M, *4(2)*–153
Davignon JP, *3(1)*–77; *4(3)*–7
Davis RD, *4(1)*–1,31,41,85
De Lena M, *6(2)*–231,381
Denck H, *4(2)*–271,275
De Palo GM, *6(2)*–231
DeVita VT, *2(1)*–23
DiDomenico E, *5(1)*–9
Di Marco A, *6(2)*–91
Dixon RL, *2(1)*–61; *3(1)*–63; *4(1)*–1
Djerassi I, *6(1)*–3
Drake JC, *6(1)*–19
Duarte-Karim M, *6(2)*–131

E

Eagan RT, *4(2)*–171; *6(2)*–335,339
Edmonson JH, *6(2)*–335,339
Eilber FR, *6(2)*–187
Einhorn LH, *6(2)*–361
Engle RR, *3(1)*–49
Ethier MF, *5(1)*–53

F

Fischer M, *4(2)*–271,275
Flamant R, *4(2)*–9
Fleischman RW, *4(1)*–31,85; *5(1)*–25,43,53
Folk RM, *5(1)*–17,37
Fonken GS, *3(1)*–7
Forcier RJ, *4(2)*–171
Fossati Bellani F, *6(2)*–231
Frei E III, *4(2)*–227; *6(1)*–25,43
Freireich EJ, *6(2)*–361
Fretts C, *4(3)*–73

G

Gasparini M, *6(2)*–231
Geil RG, *5(1)*–15
Geran RI, *3(2)*–1
Ghavimi F, *6(2)*–259
Ghione M, *6(2)*–83
Gilladoga A, *6(2)*–177,209
Glidewell O, *6(2)*–305
Goldenthal EI, *5(1)*–15
Goldin A, *4(2)*–189; *6(2)*–137
Goldman ID, *6(1)*–51,63
Goldsmith M, *6(2)*–399
Gordon MH, *5(1)*–65
Gottlieb JA, *4(2)*–227; *6(2)*–195,203,271,283,361
Gralla EJ, *5(1)*–1,79
Graw RG, Jr, *4(3)*–51
Greenberg NH, *3(2)*–1
Guarino AM, *4(1)*–1

H

Haghbin M, *6(2)*–259
Hahn RG, *6(2)*–335,339
Hall TC, *6(2)*–227
Handelsman H, *6(2)*–399
Hansen HH, *4(2)*–25,239
Hansen JL, *4(2)*–261
Harris CC, *4(2)*–43,59
Hartwell JL, *3(1)*–55
Haskell CM, *6(2)*–187
Hellmann K, *4(2)*–243
Helson L, *6(2)*–259
Henderson ES, *4(3)*–51
Henry MC, *4(1)*–41,77,97; *5(1)*–9
Heyman IA, *4(1)*–85
Hill CS, Jr, *6(2)*–283
Holland JF, *6(2)*–215,267,305
Holsti LR, *4(2)*–165
Homan ER, *3(1)*–13; *4(1)*–1
Hoogstraten B, *6(2)*–271,329
Høst H, *4(2)*–161
House R, *4(2)*–171

I

Ilievski V, *4(1)*–31,85
Israel L, *4(2)*–29,279,283

J

Jacobs SA, *6(1)*–19
Jaffe N, *6(1)*–31,43
Johnson RK, *6(2)*–137
Jonas AM, *5(1)*–1,79

K

Kanhouwa S, *4(2)*–63
Kanter PM, *6(2)*–107
Karrer K, *4(2)*–207,271,275
Kaufman DG, *4(2)*–43
Kenis Y, *6(2)*–131,343
Kintner LD, *4(1)*–51
Kokron O, *4(2)*–271,275
Korizek E, *4(2)*–271,275
Krakoff IH, *6(2)*–253

L

Lalezari P, *4(3)*–51
Lee C-C, *4(1)*–51
Lee LE, *4(2)*–7
Lefrak EA, *6(2)*–203
le Roux PLM, *4(2)*–137,157,159
Levine AS, *4(3)*–61
Levine B, *4(1)*–103,121
Livingston RB, *1(1)*–179; *4(2)*–227; *6(2)*–361
Lukeman JM, *4(2)*–79
Luthra YK, *5(1)*–53
Lutman G, *6(2)*–215
Lutz RJ, *6(1)*–19

M

Macdonald MM, *3(2)*–1
Manuel C, *6(2)*–209
Marlow M, *4(1)*–41,77,97
Marquardt H, *6(2)*–177
Marthaler T, *4(2)*–125
Masnyk IJ, *4(1)*–103,121
Matthews MJ, *4(2)*–15,63,299
Matveeva T, *4(2)*–133
Maurer LH, *4(2)*–171
Maximov T, *4(2)*–133
Menninger F, *5(1)*–43
Meryman HT, *4(3)*–51
Micksche M, *4(2)*–271,275
Milani F, *4(2)*–101
Minow RA, *6(2)*–195
Mittelman A, *4(2)*–257
Moertel CG, *4(3)*–27
Monfardini S, *6(2)*–381
Monod O, *4(2)*–245
Moon TE, *6(2)*–271
Morrison RK, *4(1)*–41
Morton DL, *6(2)*–187
Mountain CF, *4(2)*–19,307
Muggia FM, *4(2)*–69
Müller W, *4(2)*–125
Murphy ML, *6(2)*–209,259

N

Naef A-P, *4(2)*-97
Newman JW, *1(1)*-63,115

O

O'Bryan RM, *6(2)*-203,271
O'Connell MJ, *6(2)*-335
O'Connor TE, *4(3)*-79
Ogris T, *4(2)*-271,275
Oliverio VT, *2(1)*-73; *3(1)*-69; *4(3)*-13
Opelz G, *4(3)*-51

P

Parker LM, *6(1)*-25,43
Pavkov KL, *5(1)*-17,37
Pavlov A, *4(2)*-133
Penco S, *6(2)*-123
Penta JS, *6(1)*-7; *6(2)*-399
Perevodchikova NI, *4(2)*-251
Perez CA, *4(2)*-145
Perry S, *2(1)*-99
Peters AC, *5(1)*-17,37
Phelan RS, *4(1)*-85; *5(1)*-53
Philips FS, *6(2)*-177
Pickren J, *4(2)*-63; *6(2)*-215
Piczak C, *4(1)*-103,121
Pilch YH, *4(2)*-287
Pilotti S, *4(2)*-73
Pirogov A, *4(2)*-133
Pitha J, *6(2)*-203
Pitman SW, *6(1)*-25,43
Pratt CB, *6(1)*-13
Pridun N, *4(2)*-207
Prieur DJ, *4(1)*-1
Primack A, *4(2)*-1

Q

Quagliana JM, *6(2)*-271

R

Rapley LF, *4(2)*-137
Ravasi G, *4(2)*-101
Reider C, *4(2)*-271,275
Rilke F, *4(2)*-73
Rivkin SE, *6(2)*-271
Roberts D, *6(1)*-13
Robinette D, *4(2)*-63
Rodriguez VT, *6(2)*-271
Rosen G, *6(2)*-259
Rosenheim S, *6(2)*-203
Rosenkrantz H, *4(1)*-31,85
Rossi A, *6(2)*-381
Rozencweig M, *6(2)*-131,343
Rubin P, *4(2)*-311
Rymer M, *4(2)*-245

S

Saffiotti U, *4(2)*-43
Saiki JH, *6(2)*-271
Schabel FM, Jr, *3(1)*-3; *4(3)*-3
Schaeppi U, *4(1)*-31,85; *5(1)*-25,43,53
Schein PS, *5(1)*-43
Schepartz SA, *2(1)*-3
Schmid de Grüneck, *4(2)*-97
Schumacher AM, *3(2)*-1
Schwartz HS, *6(2)*-107
Sealy R, *4(2)*-137,157,159
Selawry OS, *4(2)*-1,5,177,215; *6(2)*-349,353
Shanks E, *6(1)*-13
Shields TW, *4(2)*-119
Sinkovics JG, *6(2)*-271
Sinks LF, *6(2)*-267
Skipper HE, *3(1)*-3
Slavik M, *4(2)*-265; *6(1)*-1; *6(2)*-297,399
Soper WT, *6(2)*-399
Soskolne CL, *4(2)*-157,159
Sporn MB, *4(2)*-43
Staquet M, *6(2)*-131
Sternberg SS, *6(2)*-177
Stoller RG, *6(1)*-19
Stoloff IL, *4(2)*-95
Sullivan P, *6(2)*-271
Sutow WW, *6(2)*-315
Swenberg JA, *5(1)*-17,37

T

Takita H, *4(2)*-257,293
Tan CC, *6(2)*-209,259
Tancini G, *4(2)*-231; *6(2)*-231
Tattersall MHN, *6(1)*-25,43
Taylor DJ, *4(1)*-103,121
Thigpen T, *6(2)*-271
Thompson GR, *4(1)*-31
Titscher R, *4(2)*-271,275
Tormey DC, *6(2)*-319
Trachtenberg A, *4(2)*-133
Traggis D, *6(1)*-31
Trench L, *4(1)*-103
Tucker RD, *4(2)*-157,159
Tulloh M, *4(2)*-171

U

Uslenghi C, *6(2)*-381

V

Valagussa P, *6(2)*-231
van Wyk C, *4(2)*-157,159
Venditti JM, *2(1)*-35; *3(1)*-57
Veronesi U, *6(2)*-231
Vidal PM, *6(2)*-177
Vigevani A, *6(2)*-123
Vincent R, *4(2)*-257
Volkova M, *4(2)*-133
Vollmer EP, *4(1)*-103,121

W

Walker MD, *4(3)*-21
Wallace J, *6(2)*-215
Wang JJ, *6(2)*-215,267,305
Wanka J, *6(2)*-215
Warmath EL, *6(1)*-13
Wasserman TH, *6(2)*-399
Wazeter FX, *5(1)*-15
Wiernik PH, *6(2)*-369
Wollner N, *6(2)*-209,259
Wood HB, Jr, *2(1)*-9; *3(1)*-49; *4(3)*-7
Wrba H, *4(2)*-271,275

Y

Yang KW, *4(3)*-7
Yankee RA, *4(3)*-51
Yesner R, *4(2)*-55
Young DM, *4(1)*-1; *6(2)*-159

Z

Zaharko DS, *3(1)*-21
Zelen M, *4(2)*-31,317
Zubrod CG, *2(1)*-1; *3(1)*-1; *4(2)*-3; *4(3)*-1
Zucali R, *6(2)*-381
Zwintz E, *4(2)*-207

ANNOUNCEMENTS

Conference on "Combined Modalities: Chemotherapy/Radiotherapy"

Hilton Head, South Carolina, November 15–18, 1978

The Committee for Radiation Oncology Studies, in conjunction with members of the Radiation Study Section and leading oncologists and with the support of the National Cancer Institute, is sponsoring a conference on the interaction of chemotherapy and radiotherapy. The meeting will focus on experimental results of laboratory and clinical studies of the interaction of selected cancer chemotherapeutic agents and radiation. The emphasis will be on the response of both normal and tumor tissues.

Attendance will be limited to people working in the field, certain invited speakers and participants, and those investigators who submit abstracts that are accepted by the organizing committee. It is intended to be a workshop-type meeting and abstracts will be presented either in open session or as poster-scientific exhibit sessions

Data to be presented at the meeting should meet the following criteria: (*a*) data should not have been published previously; (*b*) data must be relevant to the subjects of the meeting listed below, and (*c*) a paper must be prepared and submitted for publication at the time of the meeting, whether to be presented as an exhibit or as an oral presentation. The deadline for submission of abstracts will be August 1, 1978. Persons desiring to attend, and whose abstracts are accepted, will be eligible for partial travel support to the meeting. Additional details as to the format of the papers will be sent to those proffering accepted abstracts.

The research to be reported will include pharmacology, biochemistry, and basic chemical effects of the specific compounds, in vitro results with interaction of drug and radiation, in vivo normal tissue response to drug and radiation, and current clinical trial information. The following drugs are of special interest: bleomycin, adriamycin, cyclophosphamide, *cis*-platinum, and nitrosoureas. Papers on other agents will be considered for a session on other interesting and new agents. In addition to inviting the submission of abstracts, the organizing committee also invites nominations of young investigators who will be supported for travel to the meeting and who will not necessarily be presenting a paper.

For further details on the meeting and for abstract forms, write to: Theodore L. Phillips, MD, Chairman, Organizing Committee, Division of Radiation Oncology, University of California, M-330, San Francisco, Calif 94143.

Monograph on Non-Hodgkin's Lymphoma

A limited number of copies of the collected papers from the National Cancer Institute-CCIRC symposium on Non-Hodgkin's lymphomas which was held in San Francisco, Calif, in 1976 are available without charge. *Please contact:* Stephen E. Jones, MD, Section of Hematology-Medical Oncology, University of Arizona Cancer Center, Arizona Health Sciences Center, Tucson, Ariz 85724, in writing for a copy.

Seminars in Oncology at Roswell Park Memorial Institute

Buffalo, New York

There will be a seminar on "Progress Against Upper Gastro-Intestinal Cancer—1978" on June 8, 1978, organized by the Department of Surgery, Roswell Park Memorial Institute. The chairperson is Dr. Harold Douglass.

There is a $10.00 registration fee. *For further information contact:* Ms. Claudia Lee, Cancer Control, Roswell Park Memorial Institute, 666 Elm St, Buffalo, NY 14263.

Third Annual "Symposium on Advances in Cancer Treatment Research"

Baltimore, Maryland, May 18–20, 1978

The Baltimore Cancer Research Center, The National Cancer Institute, and the Program of Continuing Education of the University of Maryland School of Medicine are pleased to announce their Third Annual "Symposium on Advances in Cancer Treatment Research" to be conducted in Baltimore, Maryland, May 18–20, 1978, at the Baltimore Hilton Hotel.

An experienced and internationally recognized faculty will participate. This symposium is designed to update physicians and surgeons in some of the most recent developments in cancer treatment and current research including areas of clinical management, etiology, and cellular biology. Faculty members will be available throughout the symposium to discuss any questions or interests of individual course registrants. A visit to the Baltimore Cancer Research Center can be scheduled for interested persons. This course is accredited for 16 hours of Category 1 credit for the PRA of the AMA by the Program of Continuing Education, University of Maryland School of Medicine.

For further information please contact: Jack Mason, PhD, Assistant Dean for Continuing Education, 655 W Baltimore St, Baltimore, Md 21201, phone (301) 528-7422.

23rd Annual Clinical Conference on "Cancer of the Genitourinary Tract"

Houston, Texas, November 2–3, 1978

The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute in Houston, announces the 1978 Clinical Conference on "Cancer of the Genitourinary Tract" to be held at the Shamrock Hilton Hotel, Houston, Texas, November 2–3, 1978. This Conference will focus on issues of diagnosis, staging, and therapy as they relate to the critical and sometimes controversial therapies for the multiple stages of urologic malignancies. The Conference will be jointly sponsored by The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute and the American Cancer Society, Texas Division, Inc. It will provide practicing primary care physicians, oncologists, and urologists with critical issues at the moving edge of therapeutic investigation of urologic malignancies. An opportunity will be provided for speakers and registrants to exchange information at the conclusion of each session. There will be a registration fee.

This medical-education offering meets the criteria for 14 hours in Category I of the Physician's Recognition Award of the American Medical Association. This program is also acceptable for 14 prescribed hours by the American Academy of Family Physicians.

For additional information write: George R. Blumenschein, MD, Office of Education, The University of Texas System Cancer Center, M.D. Anderson Hospital and Tumor Institute, Texas Medical Center, Houston, Tex 77030.

*U.S. GOVERNMENT PRINTING OFFICE: 1978 260-909/11 1-3

If your address has changed and you wish to continue receiving this publication, please send your new address and the mailing label from this copy to:

Cancer Treatment Reports
National Cancer Institute
8300 Colesville Rd
Blair Bldg, Rm 3A05
Silver Spring MD 20910

If you do not wish to continue receiving this publication, please notify us at the address noted above and enclose the mailing label from this copy.

A publication of the National Cancer Institute

DHEW Publication (NIH) 76-22